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Selecting for Cetuximab Responders in

Advanced Head and Neck Squamous Cell Carcinoma

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute neutrophil count
BUN	Blood urea nitrogen
BRS	Biospecimen Repository Service
CBC	Complete blood count
CT	computer tomography
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IRB	Institutional Review Board
kg	kilograms
mL	milliliters
MRI	Manetic 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
SCC	Squamous Cell Carcinoma
SD	Stable disease
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 advanced head and neck SCC. The primary hypothesis is that patients who are selected by response to neoadjuvant cetuximab and go on to receive concurrent cetuximab RT will have improved 2 yr locoregional control compared to unselected patients who receive cetuximab RT. The overall treatment strategy expressed in the protocol is to treat stage III/IV head and neck SCC patients (oropharynx, larynx, hypopharynx) with 3 weeks of neoadjuvant cetuximab, select those patients who respond (develop cetuximab related folliculitis or at least a partial response by CT RECIST 1.1 criteria) and then treat them with concurrent external beam radiation therapy (EBRT) and cetuximab. Those patients who do not respond will receive concurrent cisplatinum and EBRT. The hope is that the data derived from this study will lead to a large phase II or phase III trial.

1.1 Primary Endpoint

The primary endpoint is 2 yr locoregional control in cetuximab responders. Our hypothesis is that patients who respond to neoadjuvant cetuximab and go on to receive concurrent cetuximab RT will have improved 2 yr locoregional control compared to unselected patients who receive cetuximab RT ie the cetuximab RT arm in the seminal Bonner randomized trial. The Bonner trial randomized advanced HNSCC to RT alone versus cetuximab RT.[1] The patients in the cetuximab arm were completely unselected, and had a 2 yr LRC of 50%. In the update, he noted that of the cetuximab treated patients, development of a significant rash (folliculitis) had a huge prognostic impact, with significant rash patients having a OS more than twice as long as no significant rash patients (68.8 months *vs* 25.6 months; HR 0.49, 0.34–0.72; p=0.002).[2]

Our hypothesis is that if patients are selected by response to neoadjuvant cetuximab, that those patients will have at least a 25% improved LRC over those historical cetuximab patients who were unselected. Given the difference that rash appears to make, we feel this is a very reasonable estimate.

1.2 Secondary Endpoint(s)

1.2.1 Assess secondary clinical endpoints such as the percent of patients receiving neoadjuvant cetuximab who progress by CT RECIST 1.1 criteria during the neoadjuvant cetuximab. All patients in the protocol will receive a CT with IV contrast prior and also after neoadjuvant cetuximab. Progression will be gauged using the RECIST 1.1 CT criteria for progression (at least a 20% increase in the sum of the LD of target lesions, taking as reference the pre-cetuximab scan or the appearance of one or more new lesions). If it is found that the prior probability that 20% or more of the patients are progressing during neoadjuvant cetuximab is at least 90%, the protocol will be stopped (section 16.8). The first interim analysis will be performed after 12 patients. We will also assess the 2 yr locoregional control for non-responders to neoadjuvant cetuximab. We will also assess the complete response rate to PET/CT scan 3 months after the completion of radiation therapy for both responders and for

non-responders to neoadjuvant cetuximab, as PET/CT has a NPV of 95% in this setting, so will give a very good indication of eventual locoregional control.[3]

1.2.2 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. When feasible, patients will also have another biopsy of the locoregional disease and skin after 3 weeks of neoadjuvant cetuximab but prior to starting radiation therapy. If there is a locoregional recurrence, a third biopsy of locoregional disease is possible. The second biopsy after neoadjuvant cetuximab and third biopsy in case of recurrence are strongly recommended but not absolutely necessary for participation in the protocol. Therefore, this protocol offers a unique chance to investigate molecular correlates because 1) the neoadjuvant therapy is a single agent, as opposed to a chemotherapy cocktail (and so the change in protein production is due to a single agent as well), 2) we will obtain normal tissue (skin) samples and tumor samples from before and after 3 weeks of cetuximab, so we will have in-vivo tissue to analyze after this single agent.

Our goals in the molecular analysis are to explore the following possibilities:

1. Analyze the relationship of known DNA mutations in tumor per the FoundationOne™ (or other certified genomic analysis facility) genomic profile, and correlate to clinical endpoints such as locoregional control.
2. Analyze any changes in protein production at the tumor in response to 3 weeks of cetuximab i.e., does the tumor attempt to bypass the effect of EGFR inhibitor by a) accelerating protein production downstream of EGFR receptor or b) transferring dependence to a completely different pathway from EGFR such as IGF-1R?
3. Analyze any changes in protein production at the skin in response to 3 weeks of cetuximab? Are there markers in the skin that might indicate susceptibility to develop folliculitis during cetuximab? Or do they shed light on the strong relationship between folliculitis and efficacy of cetuximab?

Molecular investigations include: 1) Genomic testing of tumor DNA using the FoundationOne™ (or other certified genomic analysis facility) genomic profile from paraffin embedded tumor samples taken before cetuximab or after locoregional/distant failure 2) RNA sequencing of tumor and skin samples from before and after cetuximab, 3) IHC analysis of EGFR downstream pathways. Of these, the first priority will be genomic testing per the FoundationOne assay, as this will be funded by the Cancer Institute of New Jersey Precision Medicine. As funds from grants or the radiation oncology department become available, the other molecular investigations may be completed.

These secondary molecular endpoints are observational, as there is very minimal data available regarding any of these questions. The study will not be powered for these molecular endpoints.

1.2.3 Image correlates: In the current protocol, the role of CT or PET/CT is to provide treatment planning and response assessment during the course of the treatment. All patients will have PET/CT imaging prior to the treatment, and after 3 months of all the treatment. There will also be CT neck with IV contrast after 3 weeks of neoadjuvant cetuximab but prior to radiation therapy. With this full panel of image set, the current protocol would allow for further study to investigate

whether the tumor imaging characteristics including anatomical and molecular parameters evaluated by PET/CT, either alone or combined with other biomarkers can attribute to the better prediction for the clinical outcomes, as 1) the response to neoadjuvant cetuximab; and 2) the final clinical endpoint, the 2-year local regional controls.

As quantification of both baseline variability and intra-treatment change is necessary to optimally incorporate functional imaging into adaptive therapy strategies, in this protocol all the image characteristics will be analyzed quantitatively. The volume, surface area and the longest diameter of the lesion will be measured based on anatomic CT image. The standard uptake value (SUV) from PET activity will be analyzed using on both region-of-interest (ROI) basis and voxel-by-voxel basis after fusing with CT. Maximum standardized uptake value (SUVmax), the peak SUV (SUVpeak within a $1cm^3$ sphere centered on SUVmax), the total SUV (SUVtotal, sum of SUV value of every voxel within the tumor region), the mean SUV within the outlined tumor region (SUVmean), the metabolic tumor volume (MTV) using 40% SUVmax as threshold and the total lesion glycolysis (TLG), from the pre-treatment PET will be calculated. Also the ^{18}F-FDG PET based tumor proliferation response (after neoadjuvant cetuximab and after the whole course of treatment) will be quantified by the change in each SUV measure relative to baseline. Univariate and multivariate analysis will be performed to identify whether imaging variables alone or combined with the clinicopathological, genomic profile, as well as the regimen choice can associate with clinical outcomes as the response to the neoadjuvant cetuximab and the response to the cocktail of the treatment. As these investigations are observational based on the amount of data will be finally collected and no power analysis is performed for this part.

2. Background and Significance

For many advanced (stage III/IV) HNSCC, the standard of care is EBRT and concurrent systemic therapy, typically either cisplatinum or cetuximab. There is ample evidence to justify either one as concurrent therapy. The MACH NC meta-analysis demonstrated a 5 year overall survival advantage of 6.5% for concurrent chemotherapy. When monochemotherapy was given, cisplatinum was superior to other chemotherapy.[4] In addition, randomized trials have demonstrated a locoregional control benefit to adding cisplatinum based chemotherapy to EBRT in advanced HNSCC[5] as well as advanced laryngeal cancer.[6]

Cetuximab is a monoclonal antibody to EGFR (epidermal growth factor receptor) that is used in combination with radiation therapy for advanced HNSCC and in combination with chemotherapy for recurrent or metastatic HNSCC. Its mechanism of action is likely dual, in that 1) it is a competitive inhibitor of natural EGFR ligands and thus prevents EGFR phosphorylation and 2) elicits ADCC (antibody-dependent cell cytotoxicity).[7,8] There is even evidence that the reponse to cetuximab may depend in part on polymorphisms in the Fc receptor on various immune effector cells[9] In combination with radiation, cetuximab may act as a sensitizer by inhibiting DNA-PK activity, thereby inhibiting double strand DNA repair.[10] A randomized controlled trial by Bonner et al in advanced oropharynx, hypopharynx and larynx SCC of EBRT + cetuximab versus EBRT alone revealed an improvement in 5 year overall survival for the cetuximab arm from 36.4% to 45.6%.[11]

For many patients, the choice of whether to choose concurrent cisplatinum or cetuximab comes down to side effects. Cisplatinum potentiates the radiation reaction, and therefore skin reaction and mucositis is clearly worse with the combination of cisplatinum and EBRT than EBRT alone. In addition, cisplatinum can also markedly decrease blood counts and cause significant nausea and vomiting. This toxicity is often severe, requiring hospitalization for pain control, IV hydration and often PEG tube insertion. On the other hand, cetuximab does not potentiate the radiation toxcities, so the rates of grade 3 mucositis and anorexia are similar to that for EBRT alone. Cetuximab does often cause a rash that is usually well managed with antibiotics, and actually correlates to improved effectiveness of cetuximab in rash positive patients. Therefore, older patients and patients with worse performance status often receive EBRT and cetuximab rather than cisplatinum, for its milder toxicity profile.

2.1 Supporting Data and Rationale

Is Cisplatinum RT or cetuximab RT better? Clearly, treating with concurrent cetuximab and EBRT is less toxic than with concurrent cisplatinum, but is it as effective? The data are conflicting. The University of Alabama recently compared 29 patients treated with cetuximab EBRT to 103 patients treated with chemotherapy EBRT. All patients were stage III to IVB. At 3 years the locoregional control was not significantly different at 70% for cetuximab and 74% for chemotherapy.[12] On the other hand, MSKCC reported on 49 patients treated with cetuximab EBRT and 125 patients treated with cisplatinum EBRT. They found that the 2 year locoregional failure was 5.7% for the ciplatinum cohort versu 39.9% for the cetuximab patients. There were several differences in the studies, the most important being that in the MSKCC study, the cetuximab patients were typically older (40.8% cetuximab group versus 5.6% cisplatinum group who were 71 yrs old or over) and with worse KPS performance status (40.8% cetuximab group versus 30.4% cisplatinum group were KPS 60-80). Most of the Alabama patients were treated on protocol, so unlike what typically happens in the community, the median KPS for the cetuximab patients was actually higher than the cisplatinum patients (median KPS of 90 compared to 80). In addition, the MSKCC study only used monochemotherapy with cisplatinum q3 weeks whereas the Alabama study used various chemotherapy regimens. The MSKCC used all IMRT (intensity modulated radiation therapy) versus conventional EBRT in the Alabama study.

Interpreting these conflicting results is difficult. Was the worse locoregional control seen in the MSKCC study due to selecting out older patients with worse performance status? Or is cisplatinum truly superior to cetuximab? The RTOG is planning to perform a randomized controlled trial of cetuximab EBRT versus cisplatinum EBRT in the future in HPV +, non smokers, but results from this trial will not be available for many years, and will not necessarily apply to HPV(-) patients or to smokers (which is the majority of patients seen at Rutgers New Jersey Medical School - Newark, who are mostly black or Hispanic). To our knowledge, no one has performed a study to assess response to neoadjuvant cetuximab and treating with either cetuximab or cisplatinum according to that response.

Is combining cisplatinum, cetuximab RT (trimodality therapy) better than cisplatinum RT? RTOG 0522 looked at this exact question in patients with stage III-IV carcinoma of the oropharynx, larynx, and hypopharynx received The experimental regimen (Arm A) consisted of

a loading dose and 6-7 weekly doses of cetuximab given in conjunction with the control arm (B) of 70-72 Gy (6 weeks) + 2 cycles of cisplatinum (q3 weeks). At 2.4 years, there were no significant differences in progression-free survival (HR [A/B]: 1.05, 0.84-1.29; *P*=0.66; 2-Y rates: 63% vs. 64%), the primary endpoint, or in overall survival (HR: 0.87, 0.66-1.15; P=0.17; 2-Y rates: 83% vs. 80%). Though only out in abstract form, as HNSCC recurrences usually occur early, this is almost certainly going to be a negative trial. Therefore, there is no rationale at this point for attempting a protocol using trimodality therapy. Per personal communication with Dr Ang (PI of RTOG 0522), he thinks that the reason that this was a negative trial was that both cisplatinum and cetuximab have the same mechanism of action: disabling of DNA repair pathways after radiation.

Determining who will respond to cetuximab on a molecular basis has been extremely difficult. Despite EGFR overexpression in up to 90% of HNSCCs, response to EGFR monotherapy has been modest.[13] In the EXTREME trial, which randomized patients with metastatic/recurrent head and neck SCC to chemotherapy versus cetuximab + chemotherapy, they noted no clear correlation between level of EGFR receptor level as determined by immunohistochemistry and response to cetuximab.[14] Notably, in the seminal Bonner trial, EGFR receptor status was not mandatory and patients were not stratified by receptor status. Nor is there a relatively simple molecular prognostic indicator of response to cetuximab, such as lack of Kras in colorectal cancer. The mutations and alternate pathways that are theorized to possibly contribute to the resistance to EGFR antagonists are numerous, including mutations in the extracellular and intracellular EGFR, K-ras and H-ras, mutations in Epithelial-mesenchymal transition such as increased vimentin expression, decreased E-Cadherin expression, decreased Claudins 4 and 7 expression, alternate pathways such as Cyclin D1 upregulation, PTEN mutations, PI3KCA mutations, Akt Amplification.[15] One relatively promising target may be EGFR variant III (EGFRVIII), which occurs in 42% of HNSCC and occurs alongside EGFRwt. Due to deletion of amino acids 6–273 of the EGFRwt extracellular domain, EGFRVIII has a truncated ligand binding site and does not bind ligand or cetuximab well. In addition, it has persistent activation of tyrosine kinase ie does not need a ligand to dimerize, and operates only via PI3k pathway (not MEK/Erk like EGFRwt). EGFRVIII is associated w increased proliferation, tumor growth and chemoresistance to anti-tumor drugs including cetuximab. Currently, phase 1 studies of immunotoxin MR1-1 targeting EGFRVIII for CNS tumors are in progress at Duke.

Currently, the picture as to what molecular marker (or more likely, combination of markers) to use to predict responsiveness to EGFR receptors is extremely confusing and complicated. As there is no clear molecular correlate to predict response to cetuximab, we chose to use a clinical response in this protocol. Below are two graphic representations of the EGFR pathway and mechanisms that may either render EGFR inhibitors ineffective or provide an alternate (downstream) mechanism to active this pathway.

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.

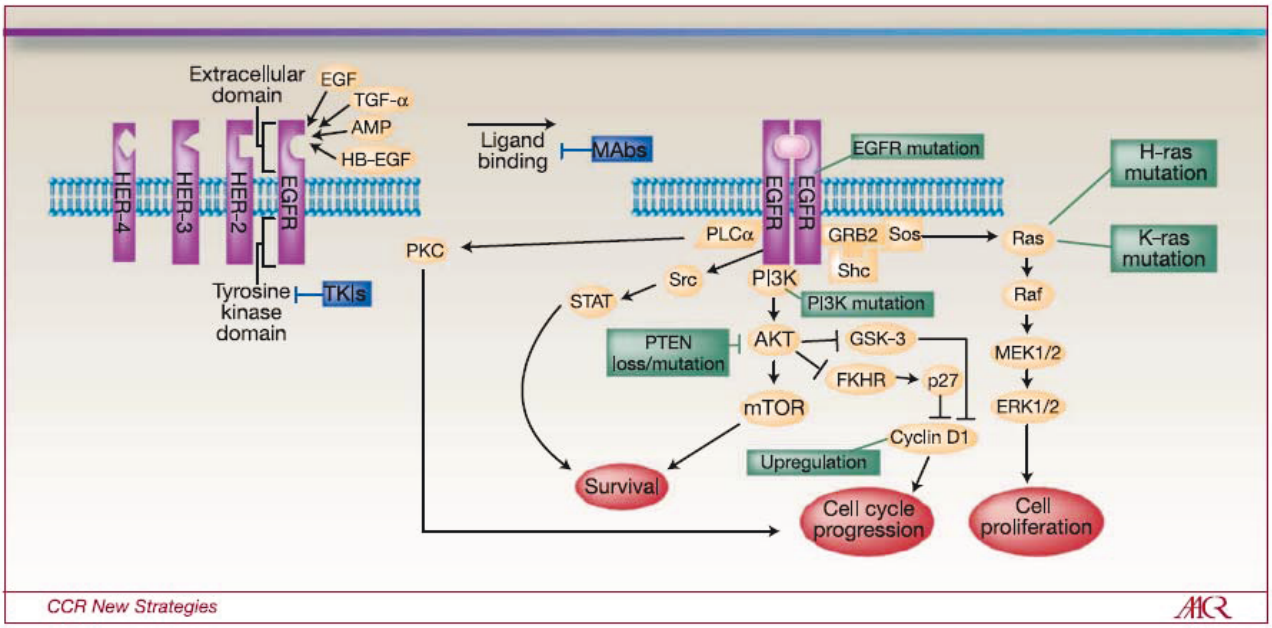


Fig. 1. EGFR signaling pathway and several mechanisms of resistance to EGFR-targeted therapies.

Kalyankrishna S, Grandis J. Epidermal Growth Factor Receptor Biology in Head and Neck Cancer. JCO 2006; 24(17): 2666-2672.

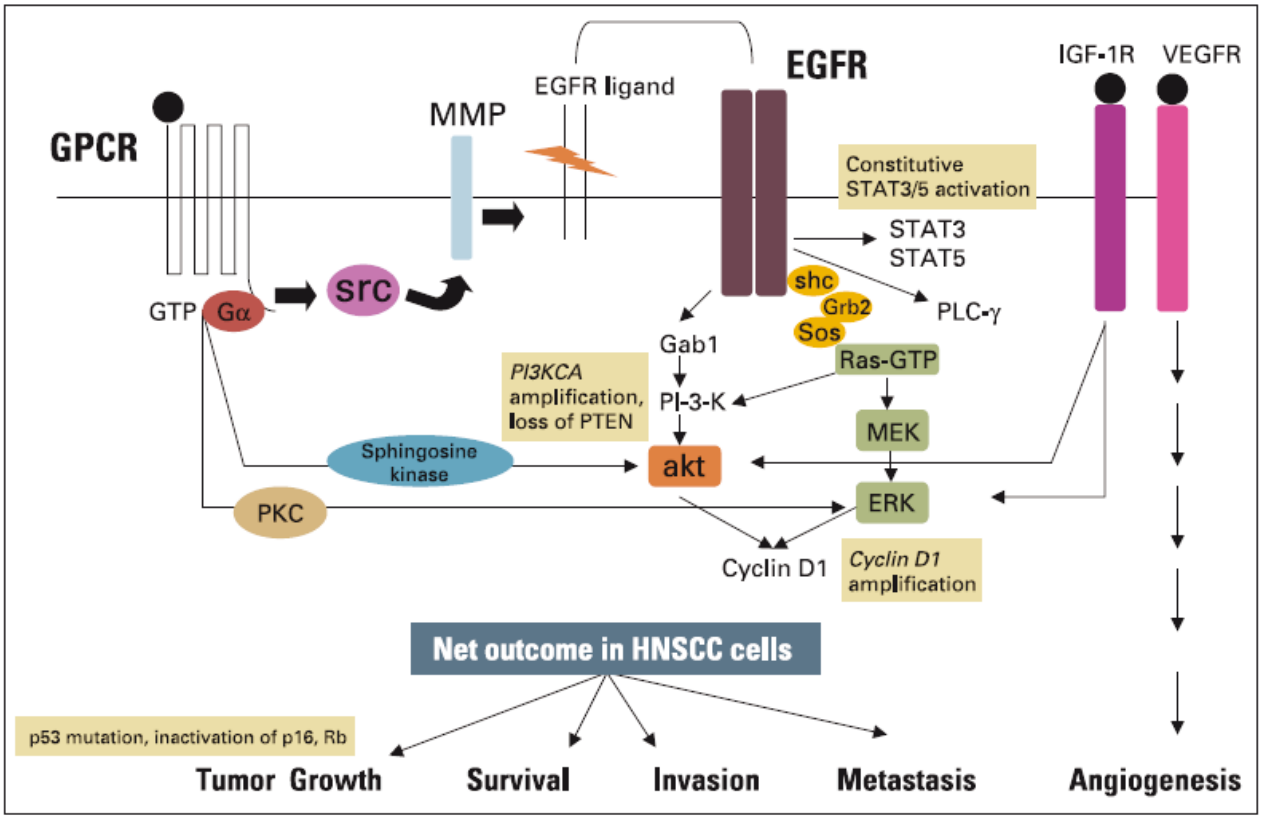


Fig 1. Possible resistance to epidermal growth factor receptor (EGFR) inhibition in head and neck squamous cell carcinoma (HNSCC) as a result of EGFR-independent activation of oncogenes. In addition to oncogenic pathways activated by EGFR, EGFR-independent oncogenesis in HNSCC may result from activation of G protein–coupled receptors (GPCRs), other growth factor receptors, genetic aberrations such as mutation and amplification of oncogenes, loss of tumor suppressor genes, and vascular endothelial growth factor (VEGF) overexpression promoting angiogenesis. MMP, matrix metalloproteinase; IGF-1R, insulin-like growth factor-1 receptor; VEGFR, VEGF receptor; PKC, protein kinase; STAT, signal transducer and activator of transcription; Rb, retinoblastoma.

What role does HPV status have on response to cetuximab?

HPV+ status has recently been shown to have a more favorable prognosis compared to HPV- patients.[16] However, it is not clear how HPV status affects response to cetuximab (note that in the seminal Bonner RCT, they did not check for HPV status, and as of yet, there is no evidence regarding how HPV status affects response to cetuximab). Since HPV+ patients clearly fare better

than HPV- patients, there is much conjecture that HPV+ patients may undergo de-escalation of therapy. However, at this point, there is no data to show that this is safe, and note that outside of this protocol in the community, most HPV+ patients would be treated with cisplatinum RT. This protocol potentially offers a rational paradigm for de-escalation of therapy, which would be ideal for the HPV+ patient. Therefore, both HPV+ and – patients are included in this protocol. HPV status is easily obtainable from RNA sequencing, so will be known for each patient.

Rash as a predictor or response to EGFR inhibitors. The only consistent indicator of how a patient will respond to EGFR inhibitors is development of rash. Below is just a sampling of evidence for a better prognosis with significant rash in response to EGFR inhibitors. What is apparent is that there is overwhelming evidence of improved prognosis in patients who develop a rash, and that this effect is consistent over different types of tumors and across different EGFR antagonists.

Author	Type of cancer	Agent	Results	Notes
Bonner[17]	HNSCC	cetuximb	Grade 2-4 rash had an OS of 68 months compared to 25 months for patients with a Grade 0/1 rash (p=0.002).	Of 208 patients receiving cetuximab and having information about rash, 174 (84%) had rash, 127 (61%) had prominent rash, and 81 (39%) had mild to no rash. Furthermore, the majority of the rash developed quickly, roughly 75% occurring in the first 2-3 weeks
Perez Soler Montefiore[18]	NSCLC, HNSCC, ovarian	Erlotinib	For NSCLC, patients with no rash, grade 1 rash and grade 2/3 rash had OS of 46 days, 257 days, and 597 days (p<0.0001). When they combined NSCLC, HNSCC, ovarian the patients with no rash, grade 1 rash and grade 2/3 rash had OS 103 days, 191 days, and 266 days (p=0.0001).	
Saridaki Z[19]	Metastatic colorectal cancer	Cetuximab	patients with no rash, grade 1 rash and grade 2 rash had time to progression of 2.3 mo, 4.5 mo, 7.5 mo (p<0.0001) and OS of 4.9 mo, 13.2 mo, 24.1 mo (p<0.0001).	
Stintzing S[20]	Metastatic colorectal cancer	Cetuximab	Patients with grade 2/3 vs 0/1 had better overall response rate (62% vs. 41%), PFS (7.8 months vs. 5.2 months) and OS (30.3 months vs. 18.0 months).	grade 0-1 was observed in 31%, grade 2-3 in 69 % of patients. First-cycle rash was observed in 66% of patients

Gatzemeier[21]	NSCLC	cetuximab	patients with no rash in 1st cycle vs those with rash in first cycle, progression free survival was 4.3 mo vs 5.4 mo (p=0.0031), and OS was 8.8 mo vs 15 mo (p<0.0001). The benefit was seen in all histologies.	acneiform rash developed in the first cycle (21 days) for 56% of the patients receiving cetuximab

Several features make rash attractive for predicting sensitivity to cetuximab in a protocol

1) It predicts response to EGFR antagonists reliably, as shown in the above table
2) It is common
   Of 208 pts receiving cetuximab and RT in the Bonner trial, 127 (61%) had prominent rash while 81 (39%) had no or mild rash
3) It happens quickly, so it can be used to make therapeutic decisions
   Most often within 2 weeks, per the Bonner trial, as illustrated below:

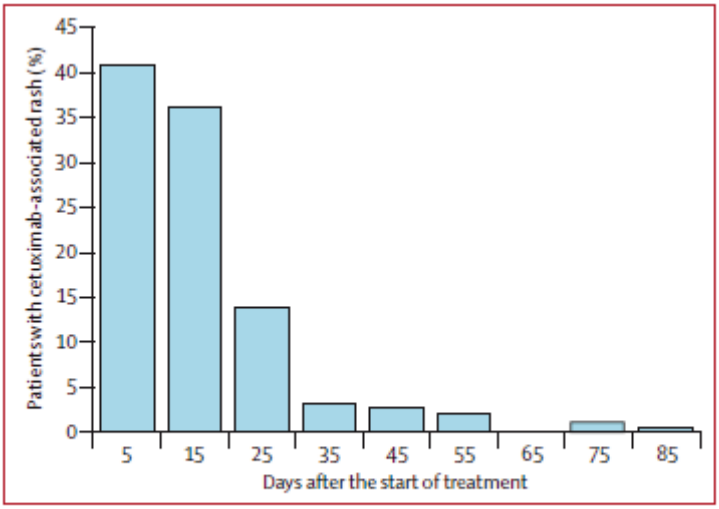


Figure 4: **The onset of cetuximab-induced rash following the initiation of first treatment**

Why do some get rash and some don't?

Some possible explanations are:

1) Is this solely a drug delivery issue i.e., some people get adequate doses of cetuximab to the skin and tumor and therefore, develop the rash and also respond at the primary tumor

site? The EVEREST (Evaluation of various erbitux regimens by means of skin and tumor biopsies) trial took patients with metastatic colorectal cancer who had previously received chemotherapy and gave them 3 weeks of irinotecan + cetuximab (400 mg/m^2 initial then weekly 250 mg/m^2). Those who failed to achieve grade 2+ rash at the standard dose (89 pts) were randomized to standard cetux dose vs. dose escalation cetux (up to 500 mg/m^2). Dose escalation did increase grade 2+ rash (59% vs. 38%) and overall response rate (30% vs. 16%) but not PFS (4.8 vs. 3.9 mo) or OS (8.6 vs. 10 mo). The response rate benefit was predictably related to Kras: in wild type KRAS the higher dose improved RR (43% vs. 30%), but had no effect on mutant KRAS (0% vs. 0%).[22] Therefore, dose escalation may increase skin rash and response, but no evidence that it will improve PFS or OS. And even in the dose escalated patients, there were still about 40% who failed to develop significant skin rash.

2) Is this an immune response issue? Several authors have demonstrated that cetuximab does rely somewhat on antibody dependent cell cytotoxicity for tumor killing. Zhen et al demonstrated that a cetuxiamb molecule with just the F(ab')2 component (missing the Fc component) had less cell killing than an intact antibody.[23] Andres Lopez-Albaitero demonstrated that Cetuximab and panitumamab apparently cannot cause antibody dependent cell cytotoxicity without the presence of peripheral blood lymphocytes.[24]

3) Is there some common susceptibility to EGFR antagonists between the skin and carcinomas? Plse see section 2.1 above under *Determining who will respond to cetuximab.*

4) Does it have to do with pattern of her family dimerization? Laux et al found that the predominant type of Her family dimerization in the skin was EGFR homodimerization in 16 patients with breast cancer. They note that EGFR-her2 heterodimerization is rare in the skin, and the reason why EGFR inhibitors cause rash and her2 inhibitors do not.[25]

How rash is used in this protocol. The essence of this protocol is to give a course of neoadjuvant cetuximab (in the Bonner trial they gave 1 week of cetuximab loading dose prior to cetuximab EBRT whereas in this protocol we give 3 weeks of neoajuvant cetuximab prior to EBRT), select out the patients who develop cetuximab associated folliculitis (section 7.2.3.1) or at least a partial response by RECIST 1.1 CT criteria, and treat those selected patients with concurrent cetuximab EBRT. Those patients who have neither a cetuximab related folliculitis or CT response will be treated with the standard cisplatinum EBRT.

We anticipate that most of the patients who qualify to receive cetuximab EBRT will do so because of the folliculitis criteria. The CT partial response criteria by RECIST 1.1 is included in case of the anticipated rare case where there is a patient who does not develop folliculitis but does respond radiographically to neoadjuvant cetuximab. This patient should clearly go on the cetuximab EBRT arm and this criteria is meant to include this patient, though we anticipate that this will occur very rarely.

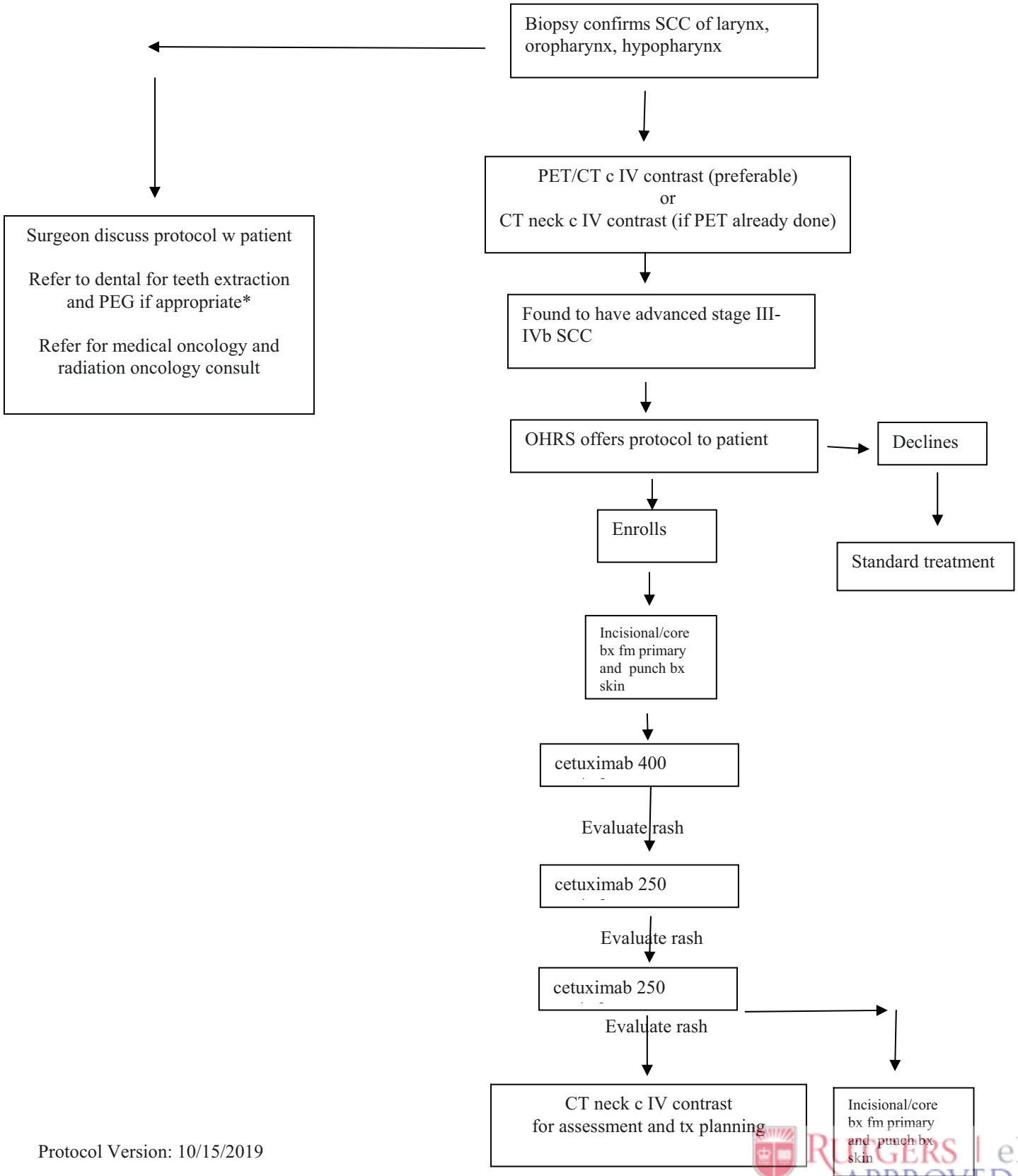
Why get a repeat biopsy after neoadjuvant cetuximab? This protocol involves a re-biopsy after the 3 weeks of neoadjuvant cetuximab. Recently, data has revealed that H&N SCC sometimes uses alternate molecular pathways as escape mechanisms. One possible pathway is the IGF-1R pathway. IGF-1R is widely present in HNSCC, and Barnes found that stimulation of head and neck cancer cells with either IGF or EGF resulted in IGF-IR and EGFR heterodimerization, but only IGF caused activating phosphorylation of both receptors. Combined treatment with A12 (IGF-1R antagonist) and cetuximab was more effective at reducing cell proliferation and migration than either agent alone.[26] There is eveidence that EGFR and IGF-1R interact on multiple levels, either through a direct association between the two receptors, by mediating the availability of eachothers ligands, or indirectly, via common interaction partners such as G protein coupled receptors (GPCR) or downstream signaling molecules. This multi-layered cross-talk may be involved in induction of resistance to targeted therapies.[27] Morgillo found that in NSCLC cell lines, that treatment with erlotinib increased the levels of EGFR/IGF-IR heterodimer localized on cell membrane, activated IGF-IR and its downstream signaling mediators.[28] With regard to radiation therapy, Ang et.al., found that in mice bearing HNSCC xenografts, that the best tumor growth delay was achieved when ganitumab (IGF-1R inhibitor) and panitumumab (EGFR inhibitor) were given concurrently with radiation. Interestingly, when the ganitumab was given with the radiation, followed by panitumamab, the tumor killing was not as effective as when the agents were given together with radiation, or when panitumamab was given with radiation, followed by ganitumab.[29]

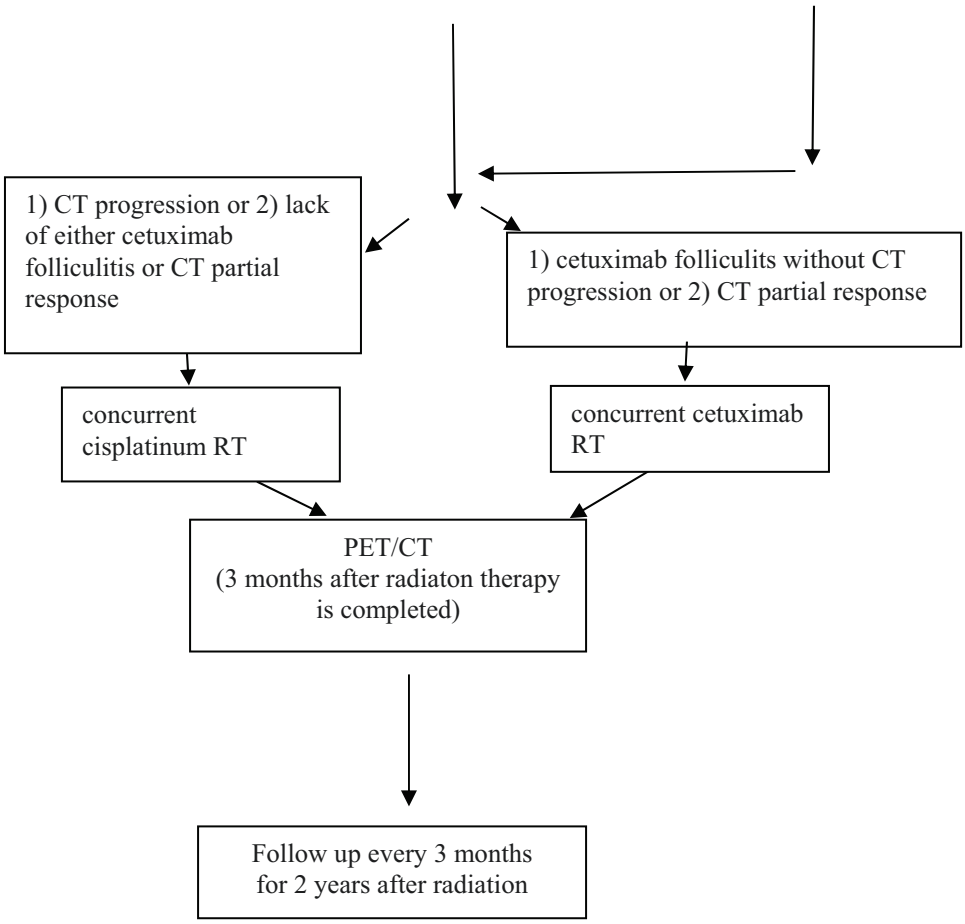
This platform, (bx before and after neoadjuvant cetuximab) is a unique opportunity to look for changes in protein or mRNA production in response to EGFR inhibitor. There are a number of protocols that have combined EGFR inhibitor with neoadjuvant chemotherapy such as TPF; however, molecular analysis of bx done after such a cocktail is difficult to interpret as there are multiple agents involved. No one to our knowledge has had such a platform to assess tumor escape pathways to just EGFR inhibitor in vivo. This may reveal IGF-1R as a significant escape pathway, or perhaps other, alternate pathways.

3. Participating Institutions

Clinical activities will take place at Rutgers New Jersey Medical School in Newark and Rutgers Cancer Institute of New Jersey. Some molecular correlative studies will be performed at Rutgers Cancer Institute of New Jersey.

4. Experimental Design and Methods





*if tooth extraction is necessary, should be extracted during neoadjuvant cetuximab or before so as not to delay radiation therapy. All patients will be encouraged to have PEG placed prior to radiation or early on in the radiation course but failure to do so will not exclude them from the protocol.

4.1 Duration of Study

The patients will be under active treatment with neoadjuvant cetuximab followed by either concurrent cetuximab EBRT or cisplatinum EBRT for approximately 3 months. Afterwards, they will be followed every 3 months for a minimum of 2 years.

We anticipate it will take 3 years to accrue and treat the patients, followed by a 2 year follow up period. Therefore, this protocol should be completed about 5 years after IRB approval.

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 Histologically proven squamous cell carcinoma of the oropharynx, hypopharynx or larynx.

5.1.2 Stage III/IVa/b SCC by AJCC 7 criteria (advanced, but not metastatic)
5.1.3 Patients must give informed consent.
5.1.4 Patients must have an ECOG performance status ≤2 (Appendix B).
5.1.5 Patients must have normal organ and marrow function as defined below:

- Platelets ≥100,000 /μL
- ANC ≥1,500 /μL
- Hemoglobin ≥ 8 g/dl (use of transfusion to achieve this is acceptable)
- Total bilirubin < 2 X institutional upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤3 X institutional ULN
- Serum creatinine <2 x institutional ULN or creatinine clearance >50 ml/min as determined by 24 hour collection or estimated by Cockcroft-Gault formula

$$\text{CCr male} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}$$

$$\text{CCr female} = 0.85 \times (\text{CrCl male})$$

5.1.6 Estimated life expectancy of at least 12 weeks.
5.1.7 Negative pregnancy test, if applicable

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 Patients may not have received previous therapy for their head and neck SCC, including chemotherapy, radiation therapy, or surgery beyond biopsy.
5.2.2 Second primary malignancy. 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), 3) non-melanomatous carcinoma of the skin
5.2.3 Patients with metastatic disease beyond the neck and supraclavicular region will be excluded
5.2.4 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. This includes scleroderma.
5.2.5 Age <18 years.
5.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cetuximab or cisplatinum or other agents used in the study.
5.2.7 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.

5.2.8 Patients with HIV infection are not automatically excluded, but must meet the following criteria: CD4 count is > 499/cu mm and their viral load is < 50 copies/ml. Use of HAART is allowed.

5.2.9 Due to a small incidence of cardiac related complications with cetuximab EBRT, patients who have had either myocardial infarction, coronary artery bypass graft, coronary artery stenting, hospital admission for heart related issues such as congestive heart failure or arrhythmia *within the last 3 months*, will not be allowed on protocol.

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

- 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;
- Magnesium < 0.9 mg/dl (< 0.4 mmol/L) or > 3 mg/dl (> 1.23 mmol/L) despite intervention to normalize levels;
- Potassium < 3.0 mmol/L or > 6 mmol/L despite intervention to normalize levels;
- Sodium < 130 mmol/L or > 155 mmol/L despite intervention to normalize levels.

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. SCC of the head and neck is exceedingly rare in this population, and they would be better treated on a pediatric protocol.

5.5 Sources or Methods of Recruitment
Patients will be recruited from Rutgers New Jersey Medical School – Newark, Doctors Office Complex and University Hospital.

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 Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institution may enter patients.

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 <u>not</u> 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.

6. Study Parameters

Evaluations	Pre-cetuximab	Weekly during neoadjuvant cetuximab	After neoadjuvant cetuximab and prior to starting radiation therapy	Weekly during radiation therapy	For first 2 months after radiation therapy	3 months after radiation therapy is completed	Follow ups every 3 months after radiation therapy for 2 years	After locoregional or distant failure
History[8], tumor assessment	X[1] (within 1 month of enrollment)	X[6]	X[16]	X[1]		X[1] (within 1 month)	X[1] (within 1 month)	X[1]
Dental Assessment	X (as early as possible, but can be done any time prior to start of RT)							
Speech Therapy Assessment	X (as early as possible but can be done any time before or during RT treatment)							
PEG Tube Assessment	X (This is done at treating physician's discretion, and can be done any time before or during RT							
Photo of rash at head, neck, upper torso put into EMR	X (1 month to 1 day prior to first cetuximab)	X						
Incisional/core biopsy of tumor	X (1 month to 1 day prior to first cetuximab)		X (any time during this interval)					X (within 2 months)
Biopsy of skin	X (1 month to 1 day prior to first cetuximab)		X (any time during this interval)					
CBC, differential, platelets	X (within 1 month to 1 day prior to enrollment)	X		X				
Serum Chemistries[2]	X (within 1 month to 1 day prior to enrollment)	X		X	X (monthly for two times +- 2 weeks)	X (within 1 month)		
Liver Enzymes[3]	X (within 1 month to 1 day prior to enrollment)		X					
Pregnancy Test[4]	X (within 1 month to 1							

	day prior to enrollment)							
Radiographic Assessments[5]	X[5]		X (CT neck w IV contrast)			X (PET/CT at 3 months +- 1 month)		X

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 3 weeks of enrollment.
5. Radiographic assessment prior to enrollment will consist of PET/CT obtained no more than 2 months prior to enrollment. CT neck w IV contrast will be obtained within 2 weeks to 1 day prior to first dose of cetuximab.
6. Assessment of rash
7. Any time during that week

7. Treatment Plan

7.1 General Considerations

The experimental aspect of this protocol is in the neoadjuvant cetuximab. Once treatment response to neoadjuvant cetuximab is established, the administration of concurrent cetuximab EBRT (with the exception that the cetuximab loading dose has already been delivered) or cisplatinum EBRT is standard. The protocol may be divided into the following phases:

7.2 Sequence of treatment

7.2.1 Prior to neoadjuvant cetuximab

Patients will be staged using PET/CT to delineate the extent of disease. Preferably, they would receive PET/CT with IV contrast so that the CT may be used to assess response to cetuximab (CT without IV contrast is not adequate for assessing the tumor or lymph nodes). In case the staging PET/CT has already been done, a CT neck with IV contrast will be ordered prior to receiving neoadjuvant cetuximab, so that the RECIST 1.1 criteria may later be applied. In case the patient cannot receive PET/CT due to insurance issues, CT neck and chest with IV contrast may be substituted.

Initial biopsy specimen (incisional/core biopsy as opposed to a FNA) will be procured from the head and neck (primary site) and punch biopsy obtained from the skin. As tissue from

the head and neck and skin will be used for DNA and RNA genotyping, tissue that is preserved and sufficient in quantity is required. So even if a patient has had a previous biopsy that is paraffin encased, a repeat biopsy may be obtained. These specimens will be handled as delineated in section 11.3.

All patients will be referred for dental evaluation. If any dental extractions are required, they should be performed early in the course (1st week preferably) of neoadjuvant cetuximab, so that radiation therapy is not delayed. Patients may be referred for PEG if appropriate. PEG should be placed during the course of neoadjuvant cetuximab or early in the course of radiation therapy, so that there is minimal esophageal mucositis at the time of PEG placement.

7.2.2 Neoadjuvant Cetuximab

Patients who agree and are eligible for this protocol will initially receive 3 weeks of neoadjuvant cetuximab. The intial dose of cetuximab will be 400 mg/m^2 IV, followed by 2 weekly doses of cetuximab 250 mg/m^2 IV. Those patients who are responders will then continue the weekly doses of cetuximab until the radiation therapy is completed.

Patients will not receive prophylactic antiobiotics prior to initiating cetuximab, so that the rash may be accurately assessed. After three weeks of neoadjuvant cetuximab or after the presence of cetuximab related folliculitis (and therefore their inclusion in the cetuximab EBRT cohort) is established, antibiotics may be prescribed. Even if a patient is found to have a cetuximab related folliculitis, they will complete the scheduled 3 weeks of neoadjuvant cetuximab.

7.2.3 Assessing for response during and after neoadjuvant cetuximab

The criteria for a positive response to cetuximab will be either 1) development of cetuximab related folliculitis or 2) CT response by RECIST 1.1 criteria. CT progression will constitute a negative response to cetuximab, regardless of folliculitis.

7.2.3.1 Cetuximab related Folliculitis

After each week of cetuximab, the patient will be assessed by medical oncology and radiation oncology for development of folliculitis characteristic of EGFR inhibition, a photo of the face and upper trunk taken and placed in their electronic medical record. Note that such photos have in the past not been routine, as nothing was done with rash information, though taking pictures of any unusual clinical features is routine (for example, cancers invading into skin). These photos will be taken by the PI, his designate or OHRS staff with a camera dedicated to taking patient pictures (not just for this protocol, but also for radiation setup checks) in the respective radiation departments, and will be put into the EMR systems (Mosaic at Rutgers New Jersey Medical School and aria at Rutgers Robert Wood Johnson Medical School). These EMR systems are password protected, and so these pictures remain confidential.

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. Unlike acne vulgaris, which is characterized clinically by both noninflammatory lesions known as comedones (blackheads and whiteheads) as well as inflammatory papules, pustules, and nodules, 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 characterized by pustular/papular appearance, usually involving the face, head, and upper torso, and often accompanied by pruritus, dry skin, and erythema[30]

In previous reports, the criteria used for significant EGFR associated rash has most commonly been grade 2+ on the CTCAE 3.0 criteria listed below. The problem with this criteria is that much of it is very subjective i.e., when exactly is intervention indicated for a rash/acne/acneiform, or how much pruritis is necessary to be intense or widespread and how can one measure pruritis beyond asking the patient how bad it is?

CTCAE 3.0 Criteria (not used in this protocol)

	1	2	3	4
Pruritus/itching	Mild or 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/acne/acneiform	Intervention not indicated	Intervention 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	-

Therefore, we chose folliculitis criteria with the goal of making it objective and reproducible, in case this protocol were to someday be expanded to a phase II or III trial. We recognize that the cost of this folliculitis criteria may be that some patients who may have had a significant rash per CTCAE 3.0 criteria may not be considered responders here; however, subjective response criteria would severely limit the value of this protocol in the future. With this in mind, the criteria for development of cetuximab related folliculits is:

Development of folliculitis characterized by a pustular/popular appearance located on the face, head, or upper torso (examples in appendix C).

7.2.3.2 CT response by RECIST 1.1 criteria

The week after the 3rd dose of neoadjuvant cetuximab (Day 14-21 after the first dose of cetuximab), the patient will have a CT neck with IV contrast for comparison to the first CT neck performed prior to neoadjuvant cetuximab. CT response will be evaluated using RECIST 1.1 1.1 criteria: (E.A. Eisenhauer et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). EUR J CANCER 4 5 (2 0 0 9) 2 2 8 –2 4 7].

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sumdiameterswhile on study

Please note that significant changes from version 1.0 include for malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

7.2.4 Repeat Bx after neoadjuvant cetuximab. After 3 weeks of neoadjuvant cetuximab, a biopsy specimen (incisional/core biopsy as opposed to a FNA) will be procured from the head and neck primary site). As this tissue will be used for DNA and RNA sequencing, tissue that is preserved and sufficient in quantity is required. These specimens will be handled as delineated in 11.3.

7.2.5 Determining treatment modality

The patients who receive cisplatinum RT will be those who

1. progress by CT RECIST 1.1 criteria during neoadjuvant cetuximab, regardless of rash
2. do not develop either a cetuximab related folliculitis or a partial response by CT RECIST 1.1 criteria

The patients who receive cetuximab RT will be those who

1. develop a cetuximab related folliculitis (at any point following the first cetuximab dose and prior to starting EBRT) without CT progression (ie stable or partial response)
2. have at least a partial response by CT RECIST 1.1 criteria

The dependence of treatment modality on CT response and rash is illustrated by the below table:

CT response by RECIST 1.1

		Progressive disease	**Stable disease**	**Partial response**
Rash	**(-)** cetuximab related folliculitis	**Cis RT**	**Cis RT**	**Cetux RT**
	(+) cetuximab related folliculitis	**Cis RT**	**Cetux RT**	**Cetux RT**

7.2.6 Concurrent cetuximab and EBRT

Patients receiving cetuximab EBRT will receive concurrent cetuximab 250 mg/m^2 IV weekly during the duration of EBRT. There will be no breaks in weekly cetuximab delivery i.e., patients will receive weekly cetuximab from the first dose of neoadjuvant cetuximab to the end of radiation therapy (except when discontinued for toxicity). Patients will be seen and assessed weekly by radiation oncology and medical oncology.

7.2.7 Concurrent cisplatinum and EBRT

Patients receiving concurrent cisplatinum EBRT will receive 100 mg/m^2 q 3 weeks during EBRT or alternatively, 40 mg/m^2 weekly during EBRT. The q 3 weeks regimen is preferable, but the weekly regimen may also be used, at the discretion of the treating medical oncologist. The EBRT technique will be identical to that used for concurrent cetuximab and EBRT. Patients will be seen and assessed weekly by radiation oncology and on a regular basis by medical oncology, how frequently depending on the cisplatinum regimen.

7.3 External Beam Radiation Therapy

The EBRT will be performed either at Rutgers New Jersey Medical School - Newark or RWJUH radiation oncology, using either 3 dimensional conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT). Tomotherapy is considered a form of IMRT. IMRT will be performed using 3 different dose levels applied to 3 target volumes: PTV1 (70 Gy in 33 fractions), PTV2 (60 Gy in 33 fractions) and PTV3 (54 Gy in 33 fractions). 100% of the dose will be prescribed to at least 95% of the PTV volume.

Tolerances for normal structures will be observed at the following limits:

Brainstem + 0.5 cm	maximum 54 Gy
Spinal cord + 0.5 cm	maximum 50 Gy

Mandible	maximum 70 Gy
Parotids*	mean 26 Gy

*Parotids will be spared depending on proximity to pathologic lymph nodes

In certain cases, the location of the tumor will make these limits impossible to achieve, and patients will be planned at the discretion of the treating radiation oncologist.

7.3.1 Dose Modifications or Escalations
Treatment breaks will be granted only in case of severe grade 3 / 4 toxicity per the discretion of the treating radiation oncologist.

7.3.2 Hematologic Toxicity
The amount of bone marrow affected by head and neck radiation therapy is very small, and has minimal effect on hematologic toxicity. Radiation therapy will not routinely be held for hematologic toxicity, except at the discretion of the treating radiation oncologist.

7.3.3 Non-Hematologic Toxicity

7.3.3.1 Mucositis. Patients may require analgesia with narcotic agents during and after radiation therapy. They will be started on short acting agents such as oxycodoene or percocet and may require long acting medication such as Oxycontin or fentanyl patch as well. They may also receive other soothing mouthwash prescriptions. Patients will be encouraged to have a PEG placed prior or early in the course of radiation therapy, though failure to do so will not exclude them from this protocol.

7.3.3.2 Change in Taste
This is an expected side effect and patients will be advised accordingly that despite change in taste, that they must continue to take in sufficient calories to maintain their weight as much as possible.

7.3.3.3 Dry mouth. Patients will be encouraged to use frequent baking soda and water mouth rinses as well as mouth moisturizing products like Biatene spray.

7.3.3.4 Skin reaction. Patients will be encouraged to apply Vaseline based cream such as aquaphor on neck at least twice daily.

7.3.4 Adherence/Compliance
Patients who do not adhere to their radiation oncologists recommendations regarding daily radiation treatments may be removed from the study.

7.4 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.

7.4.1 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.

$$BSA\ (m^2) = \sqrt{\frac{(height)x(weight)}{3131}}$$

For the determination of body surface area, height is measured in inches and weight is measured in pounds.

7.4.2 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.

During radiation therapy, weekly dose is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of radiation therapy (6–7 weeks). 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.

7.4.3 Dose Modifications or Escalations

7.4.3.1 Infusion Reactions

Serious infusion reactions occurred with the administration of Erbitux 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 with 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, requiring medical intervention and/or 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 medical intervention and 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 Erbitux 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 Erbitux 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.
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.

7.4.3.2 Rash: 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 Erbitux therapy. Acneform rash occurred in 76–88% of 1373 patients receiving Erbitux in clinical trials. Severe acneform rash occurred in 1–17% of patients.

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 Erbitux for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during Erbitux therapy.

Rash occurring outside the radiation field 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% BSA; spontaneous bleeding	
Rash/acne/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 ADL	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
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	-	-	-

Rash occurring inside the radiation field may be graded according to the following table from CTCAE 4.0:

	1	2	3	4
Dermatitis associated with 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

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

Occurrence of severe (grade ¾) acneform rash	Cetuximab modification
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

7.4.3.3 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.

7.4.3.4 Hematologic Toxicity

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

7.4.3.5 Non-Hematologic Toxicity

See above

Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and Erbitux as compared to none of 212 patients treated with radiation therapy alone in a randomized, controlled trial in patients with SCCHN. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of Erbitux. One patient with no prior history of coronary artery disease died one day after the last dose of Erbitux. Carefully consider use of Erbitux in combination with radiation therapy in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux.

Pulmonary Toxicity

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

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 Erbitux therapy. Acneform rash occurred in 76–88% of 1373 patients receiving Erbitux in clinical trials. Severe acneform rash occurred in 1–17% of patients.

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 Erbitux for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during Erbitux therapy.

Hypomagnesemia and Electrolyte Abnormalities

In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients (199/365) receiving Erbitux 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 Erbitux. Periodically monitor patients for hypomagnesemia,

hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of Erbitux. Replete electrolytes as necessary.

7.4.4 Concomitant Medications

There are no concomitant medications that are contraindicated with cetuximab.

7.4.5 Supportive Care Guidelines

7.4.5.1 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: As this protocol depends on grading of rash, prophylactic antibiotics may not be used until 3 weeks of neoadjuvant cetuximab has been received and rash assessed, or cetuximab related folliculitis has been determined. 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: As this protocol depends on grading of rash, prophylactic Benadryl or Atarax may only be used as necessary during infusion, but not otherwise, until 3 weeks of neoadjuvant cetuximab has been received and rash assessed, or cetuximab related folliculitis has been determined. Benadryl or Atarax may be helpful to control itching.

Topical Steroids: The benefit of topical steroids is unclear. They will not be used prophylactically.

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

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.[31]

7.4.6 Adherence/Compliance

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

7.5 Study Agent (Cisplatinum)

Cisplatinum is known to bind to DNA and produces inter-strand cross links. It is thought that the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH. Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. Refer to package insert for additional information.

7.5.1 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.

$$\text{BSA } (m^2) = \sqrt{\frac{(height)x(weight)}{3131}}$$

For the determination of body surface area, height is measured in inches and weight is measured in pounds. If a weight change of ≥ 10% occurs, the cisplatin dose should be recalculated.

7.5.2 Treatment Administration

Patients who do not respond to or progress through neoadjuvant cetuximab will receive cisplatin, 100 mg/m^2, administered intravenously on approximately Days 1, 22 and 43 of radiation therapy. Days of administration may vary up to two days, and may vary longer if necessary due to toxicity. Alternatively, at the treating medical oncologist's discretion, the patient may instead receive weekly cisplatinum 40 mg/m^2. Note that in order to receive the full dose cisplatin 100 mg/m^2, the original GFR must be > 60 ml/min. To receive the cisplatinum 40 mg/m^2, the original GFR must be >50 ml/min.

High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional guidelines for highly emetogenic regimens

should be followed. In the absence of such guidelines:

For acute nausea and vomiting, premedication should include a 5-HT3 antagonist, such as granisetron, ondansetron, or palonosetron, plus a corticosteroid, such as dexamethasone, up to 20 mg *i.v.*. Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist. Delayed nausea and vomiting (greater than 24 hours after chemotherapy administration) may be managed by the addition of aprepitant concurrently or with metoclopramide and dexamethasone.

Patients must receive vigorous hydration and diuresis. A suggested regimen is prehydration with a 1 liter of D5N S over 2-4 hours and mannitol, 12.5 g *i.v.* bolus immediately prior to cisplatin. Then cisplatin, 100 mg/m^2, in 500 ml NS is administered over 1-2 hours with an additional 1 to 1.5 liters of fluid given post-hydration. Any pre-existing dehydration must be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for management. Overnight hospitalization for hydration after cisplatin is strongly encouraged if it is allowed by the patient's insurance company. Additional *i.v.* hydration and BUN/creatinine check should be strongly considered later in the week after cisplatin administration, in order to prevent dehydration and severe fluid/electrolyte imbalance.

7.5.3 Dose Modifications or Escalations

If cisplatin dose is held due to toxicity, CBC should be repeated weekly until counts recover to minimum levels required to resume treatment. If the dose of cisplatin is delayed more than 21 days because of hematologic or renal adverse events, that dose will be omitted.

7.5.3.1 Hematologic Toxicity

If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200, hold treatment until ANC ≥ 1200, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction. Per CTCAE, v. 4.0, febrile neutropenia is fever of unknown origin without clinically or microbiologically documented infection; ANC < 1.0 x 10e9L, fever > 38.5°C.

Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is <75,000, hold treatment until platelets are > 75,000, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction.

7.5.3.2 Non-Hematologic Toxicity

Renal Adverse Events: Cisplatin should be administered on the scheduled day of treatment using the following guidelines: If creatinine is > 1.2 mg/dl, clearance must be done in order to make dose adjustment. If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the nomogram calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

Creatinine clearance	Cisplatin dose
> 60 ml/min	100 mg/m^2
40-50 ml/min	50 mg/m^2
< 40 ml/min	Discontinue and notify PI

***Neurotoxicity*:** If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin. The radiation therapy will continue.

Mucositis: Grade 4 will require a 25% dose reduction

Ototoxicity*:* For new clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living, treat at 50% dose reduction. For hearing loss requiring a hearing aid, discontinue cisplatin. If the physician is unsure about the severity of the hearing loss, an audiogram is encouraged.

7.5.4 Concomitant Medications

Patients are discouraged from taking excessive antioxidants while on this study, as it theoretically should lessen the efficacy of radiation therapy, but this should not exclude anyone from being on study.

7.5.5 Supportive Care Guidelines

Patients are allowed to receive full supportive care therapies concomitantly during the study. No other chemotherapy, immunotherapy, hormonal cancer therapy, radiation therapy, surgery for cancer, or experimental medications will be permitted while the patients are participating in this study.

Antiemetic agents

Premedication with a 5HT3 antagonist and corticosteroid is encouraged as discussed in Section 7.4.3.1.

Colony stimulating factors (CSFs)

CSFs are not permitted as primary prophylactics. If, in the Investigator's opinion it is required in the presence of severe neutropenia (ANC <500/µl for at least 3 days) with or without the presence of documented infection then use of CSFs must be discontinued at least 24 hours prior to the start of the next cycle of chemotherapy. If a patient develops hematologic toxicities, chemotherapy dose reduction and acute treatment of neutropenia are

recommended, rather than chemotherapy dose maintenance and pre-emptive treatment with CSFs.

Erythropoeitin use is not permitted as it has been demonstrated to have a detrimental effect on HNSCC tumor control. Blood transfusions are permitted at the oncologists' discretion.

7.5.6 Adherence/Compliance

Patients will receive cisplatinum q 3 weeks or weekly per their medical oncologist. They should adhere to their oncologist's recommendations (based on the protocol) re administration of cisplatinum. 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. Grade 2 and above toxicities will be recorded.

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.

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 Office of Human Research Services at (732) 235-9565. 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.

During the radiation phase of treatment, they are seen weekly by the treating radiation oncologist, who can report any applicable toxicities.

During the 3 weeks of neoadjuvant cetuximab, the patients must still be seen weekly by radiation oncology at either Robert Wood Johnson University Hospital (RWJUH) or Rutgers New Jersey Medical School, in order to evaluate for folliculitis. In this manner, the patients may thus be monitored for toxicity weekly.

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 or cisplatinum 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.

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 and neck by CT using RECIST 1.1 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 [*JNCI* 92(3): 205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 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 7.2.3.1

9.2 Evaluation of CT response at primary site and neck

CT scans of the neck with IV contrast will be taken before and after neoadjuvant cetuximab (Day 14-21 after the first dose of cetuximab). At the primary site and neck lymph nodes, the largest diameter on axial CT slices will be measured and recorded. All measurements will be taken and recorded in metric notation using measuring software in the applicable radiology programs. In all possible cases, spiral CT (as opposed to standard CT) will be performed. Response will be graded per RECIST 1.1 criteria: [E.A. Eisenhauer et al. New response evaluation criteria in solid tumours: Revised RECIST 1.1 guideline (version 1.1). Eur J Cancer 4 5 (2 0 0 9) 2 2 8 –2 4 7].

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Please note that significant changes from version 1.0 include for malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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 or after locoregional/distant failure
2. RNA sequencing of tumor samples before and after cetuximab
3. RNA sequencing of skin samples before and after cetuximab
4. DNA sequencing of tumor and skin samples before and after cetuximab
5. IHC analysis of EGFR downstream pathways that are illuminated by the above

The laboratory investigations are very comprehensive, ranging from partial DNA sequencing (FoundationOne™ (or other certified genomic analysis facility)) 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™ (or other certified genomic analysis facility) is targeted DNA sequencing that is performed on paraffin embedded tumor samples As a pan-cancer test, FoundationOne™ (or other certified genomic analysis facility) 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.[32] [33] 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. In addition, HPV status can be easily determined from RNA sequencing. Once the cDNA library is created by Cancer Institute of New Jersey Functional Genomics (Curtis Krier), analysis will be performed by Cancer Institute of New Jersey bioinformatics (Jeffrey Rosenfeld).

11.2 Tissue to be collected

All patients must have a diagnosis of squamous cell carcinoma (SCC) prior to entering into this protocol, and this diagnosis is typically achieved by a biopsy from either the primary site or FNA from a neck lymph node. However, this protocol requires additional biopsies as 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 a paraffin embedded block which will be sent to FoundationOne™ (or other certified genomic analysis facility) for DNA sequencing and analysis of genetic mutations.
2. Providing frozen tumor to Cancer Institute of New Jersey Functional Genomics Facility for RNA sequencing
3. Providing skin tissue to Cancer Institute of New Jersey Functional Genomics Facility for RNA sequencing

Thus, all patients on the protocol will have prior to the neoadjuvant cetuximab, an incisional/core biopsy from the primary site and a skin punch biopsy (from the neck or upper trunk), 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. The primary site is favored over a neck lymph node as the biopsy site, as an incisional or core biopsy runs some small risk of seeding the skin of the neck.

After neoadjuvant cetuximab, an additional bx will be obtained from the primary site- because this tissue will only be used for RNA sequencing (and not sent to FoundationOne™ (or other certified genomic analysis facility) for DNA analysis), 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 ie 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 is possible, and again paraffin-embedded sample will be sent to FoundationOne™ (or other certified genomic analysis facility) for analysis, and fresh tissue may be obtained for RNA sequencing.

Note that these supplemental biopsies (excluding the biopsy establishing a diagnosis of SCC) are highly encouraged, but are not absolutely necessary for participation in the protocol.

11.3 Collection and Handling Procedures at Rutger New Jersey Medical School

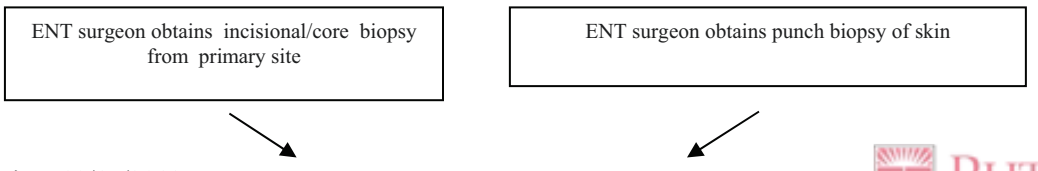
a. OHRS will coordinate with otolaryngology regarding the date and time of pending biopsies. These biopsies will consist of pre-cetuximab primary site tumor and skin biopsies, followed on a later date, by post-cetuximab primary site tumor and skin biopsies. The procedures for obtaining, processing, and transporting these specimens are identical for pre and post-cetuximab biopsies. Note that these biopsies are for research purposes only, as the patient must already have pathologically proven SCC in order to qualify for this protocol, and that these additional biopsies do not in any way determine how the patient will be treated. Accordingly, these additional biopsies will not pass through Rutgers New Jersey Medical School- Newark pathology, but instead will be stored and transported to Rutgers CINJ BRS.

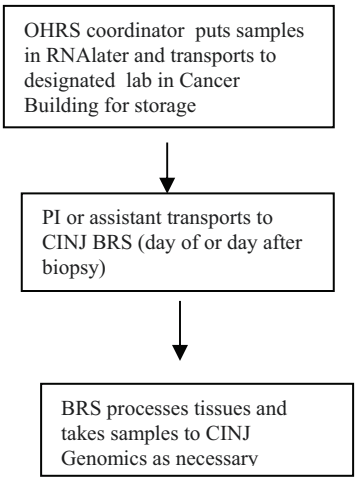
b. Otolaryngology
    a. (Drs Baredes, Park or designate) will obtain incisional/core biopsy from the primary site. In order to biopsy for this protocol, the primary site must be accessible without the need for endoscopy, anesthesia or operating room ie these will mostly be oropharyngeal primaries. Ideal size of the tumor specimen is 0.5 cm x 0.5 cm (though it is recognized that this may not be possible for most specimens, and there will be some degree of trial and error for the first few patients in terms of adequate tissue for RNA sequencing).
    b. ENT will also obtain a skin punch biopsy from the neck, shoulders or upper chest. If the above biopsy from the primary site is not obtainable, the skin biopsy will still be obtained.
c. Transport from otolaryngology to storage
    a. OHRS (Zhiwei Yin or designate) will keep specimens moist and cool, with wet paper towel and ice over specimens to minimize RNA degradation while transporting, and then will place specimens in a cryo-vial with RNAlater. Before immersion in RNAlater, cut large tissue samples to ≤0.5 cm in any single dimension, and then place the fresh tissue in 5–10 volumes of RNAlater. The cryo-vial should be labeled with the study patient sequence number, date received, and the words “Pre (or Post)-drug tumor bx in RNAlater” and placed in 4°C refrigerator in a designated lab in the Cancer Building.
d. Transportation from designated lab in Cancer Building to CINJ BRS
    a. On the same day or the day after biopsies are taken, the PI, Zhiwei Yin or Stephen Sozio will take the above tissue samples from the designated lab in the Cancer Building and deliver to CINJ BRS. Primary tumor samples and skin samples will be transported in an approved container with wet ice. Every effort will be made to transport within 1-2 days, but 3 days will be allowed in exceptional situations.
e. Handling of tissues at Rutgers CINJ BRS
    a. The primary tissue specimen will be split into two pieces. One part of the primary tissue specimen will be placed in a cryo-vial with **RNAlater**. Before immersion in RNAlater, cut large tissue samples to ≤0.5 cm in any single dimension, and then place the fresh tissue in 5–10 volumes of RNAlater. The cryo-vial should be labeled with the study patient sequence number, date

received, and the words "Pre (or Post)-drug tumor bx in RNAlater" and placed in 4°C refrigerator. When ready to freeze, these biopsies will have the supernatant removed and be placed into -80 freezer for storage. Periodically, these frozen tissues will be delivered to Genomic Facility (Kurtis Crier or designate) by the BRS.

b. Another part of the primary tissue specimen will be put into **formalin** with the study patient sequence number, date received, and the words "Pre (or Post)-drug tumor bx in formalin." This specimen will subsequently be made into a paraffin block. The paraffin block containing Pre-drug tumor biopsies will be verified to have SCC by a qualified pathologist and then sent to FoundationOne™ (or other certified genomic analysis facility) once funds are available. The paraffin block containing Post-drug tumor will be verified to have SCC by a qualified pathologist and stored for IHC.
    i. In case the paraffin block is found to not contain SCC, then the corresponding tumor sample in RNAlater may be examined for SCC. If no SCC is found in either sample, then none of these samples will be sent to the CINJ Genomic Facility or to FoundationOne™. Repeat tumor biopsies will not be performed in this case. However, if the pre-cetuximab tumor sample is devoid of SCC, the post-cetuximab tumor biopsy will still be obtained and processed.
    ii. If no research tumor biopsies are performed (beyond that required for diagnosis) or all research tumor biopsies are devoid of SCC, Rutgers NJMS pathology will supply the tumor specimen in paraffin block used for diagnosis for possible analysis by FoundationOne™.
c. The cryo-vial with skin biopsy should be labeled with the study patient sequence number, date received, and the words "Pre (or Post)-drug skin biopsy" and placed in 4°C refrigerator. When ready for freezing, these biopsies will have the supernatant removed and be placed into -80 freezer for storage. Periodically, these frozen tissues will be delivered to Genomic Facility (Kurtis Crier or designate) by the BRS.

Rutgers New Jersey Medical School - Newark BIOPSY FLOWCHART
(Applicable for both pre and post cetuximab tissue samples)





11.3.1 Handling of tissue at Cancer Institute of New Jersey Functional Genomics Facility

Clinical samples will be sent to:

Curtis Krier (or designate)
Manager
Functional Genomics Facility, Cancer Institute of New Jersey
125 Paterson Street, CAB 7050, Robert Wood Johnson Medical School, New Brunswick, NJ 08901
Phone (732) 235-6426

1. **Extraction of total RNA**
   Total RNA from fresh frozen tissues will be extracted using RNeasy mini kit (QIAgen) according to the manufacturer's instructions. Total RNA from FFPE samples will be extracted using RNeasy FFPE kit (QIAgen). Concentration of RNA will be measured using Qubit 2.0 fluorometer (Invitrogen) and the quality will be examined with RNA 6000 Nano assay kit and Bioanalyzer 2100 (Agilent).

2. **Extraction of Genomic DNA**
   Genomic DNA from fresh frozen samples will be extracted using DNeasy blood and Tissue kit (QIAGEN) according to the manufacturer's instructions. Genomic DNA from FFPE tissue samples will be extracted using QIAamp DNA FFPE Tissue Kit (QIAGEN). The concentration genomic DNA will be measured using Qubit 2.0 Fluorometer (Invitrogen) and the quality will be assessed with Agarose gel electrophoresis.

3. **RNA Seq library preparation from Fresh frozen sample**
   RNA seq library will be constructed using Illumina TruSeq RNA sample preparation v2 protocol and the pooled libraries will be sequenced on the Illumina HiSeq 2000.

4. **RNA Seq library preparation from FFPE sample**

RNA seq library will be constructed using ScriptSeq complete gold kit (Epicentre) and the pooled libraries were sequenced on the Illumina HiSeq 2000.

5. **Whole-exome sequencing**
   Whole-exome sequencing will be carried out using Illumina TruSeq Exome Enrichment protocol. Whole genome library will be constructed first using Illumina TruSeq™ DNA Sample Preparation v2 protocol. The fragmented DNA from each sample will be then enriched with TruSeq Exome enrichment protocol. Enriched fragments will be amplified using PCR. The bar coded libraries will be examined by Qubit for DNA amount and Agilent Bioanalyzer for DNA fragment size distribution, then diluted to appropriate molar concentration. Pooled libraries will be sequenced on the Illumina HiSeq 2000.

6. **Cluster Amplification and Sequencing**
   Cluster amplification of denatured templates will be performed on cBot according to the manufacturer's protocol (Illumina) using HiSeq 2000 v2 cluster chemistry and flowcells. Flowcells will be sequenced on HiSeq 2000 using HiSeq 2000 v2 Sequencing-by-Synthesis Kits, then analyzed using RTA v1.10.15. or RTA v.1.12.4.2. Raw sequencing data will be processed into read sequences and base quality scores using the standard Illumina pipeline.

7. **Validation Experiments**
   RNA seq data will be validated with QPCR. TaqMan probes and primers (ABI) for selected genes will be used for validation purposes.

   DNA seq data will be validated with selected mutations using 1 to 20 ng genomic DNA. TaqMan SNP genotyping assay (ABI) will be used for the validation studies.

   QPCR will be performed on the Stratagene Mx 3005P QPCR machine (Agilent) according to manufacturer's instructions.

11.3.2 Process at Cancer Institute of New Jersey Bioinformatics

DNA and/or RNA sequencing will be performed using established procedures at Cancer Institute of New Jersey, including standard protocols for DNA/RNA extraction, library preparation, and sequencing on Illumina HiSeq 2000 or similar technology.

Mutational status of each sample can be determined from both DNA and RNA sequencing, while gene expression may only be detected from RNA sequencing. We will aim for at least 50X coverage curing DNA sequencing or at least 20 million reads during RNA sequencing. We have previously shown that latter is sufficient for unambiguous detection of HPV
infection in known hosts, such as HeLa cell lines.

Genomic analysis will be performed using established pipelines at the Cancer Institute of New Jersey. Initial read alignment to the reference hg19 human genome will be done using BWA,

Bowtie2 and/or TopHat packages. Low quality reads will be filtered using standard Illumina protocol, allowing for minimum phred score of 25 per base. Genomic variants, including single nucleotide variants, and small insertions and deletions, will be called using GATK package following Broad Institute Best Practices Variant Detection protocol. Larger deletions and insertions, including exon and whole gene amplifications, will be analyzed based on changes in coverage using in-house pipelines. Changes in gene expression levels will be analyzed using Cufflinks, IPA, as well as in-house tools and pipelines that are part of local package iSeek. All detected variants and changes in gene expression will be compared with known databases, such as COSMIC, TCGA, IPA, and others.

12. Pharmaceutical Information

12.1 Investigational Agents

There are no investigational agents involved in this study.

12.2 Commercial Agents

Product description: Cetuximab is commercially available from Merck, IMCLONE. In this protocol cetuximab is not supplied, and is paid for by the patient or his insurance company.

Preparation: Erbitux® (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 Erbitux 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:

- 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 Erbitux 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 NCI's CTMS case report forms, in electronic format (e-CRFs) will be utilized. Completion of the e-CRFs will be done in accordance with the instructions provided by Cancer Institute of New Jersey, the coordinating center in a study-specific data capture plan. Electronic CRFs will be submitted to the OHRS via Cancer Institute of New Jersey's On-line Clinical Oncology Research Environment (ONCORE). The e-CRFs are found in the study specific calendar that has been created in ONCORE. The system will prompt the user to the forms that are required based upon the patient's enrollment and treatment dates.

The Principal Investigator will be responsible for assuring that all the required data is entered onto the e-CRFs accurately and within 2 weeks of the date in which the previous cycle was completed.

Periodically, monitoring and/or auditing visits will be conducted by staff from the Coordinating Center. The Principal Investigator at each participating center will provide access to his/her original records to permit verification data entry.

Case report form completion instructions and training will be provided to each participating institution before study activation at the participating institution.

13.2 Research Charts

A research chart will be maintained for each patient enrolled. Copies of the most 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, demographics, time to progression and survival. This information will be updated on a prospective basis and will be confidentially maintained at the OHRS.

14. Data and Safety Monitoring

Monitoring of this study will occur in accordance with the Cancer Institute of New Jersey's NCI approved Data and Safety Monitoring Plan (DSMP). An "initiation audit" will be conducted at Cancer Institute of New Jersey 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. All centers will be monitored at least quarterly and audited annually. 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 Cancer Institute of New Jersey's Human Research Oversight Committee and the PI.

15. IRB Approvals

This protocol will enroll patients from Rutgers New Jersey Medical School and Rutgers Cancer Institute of New Jersey. Some molecular correlate studies will be performed at Rutgers Cancer Institute of New Jersey.

16. Statistical Considerations

16.1 Primary Hypothesis

The primary hypothesis is that patients who respond to neoadjuvant cetuximab and go on to receive concurrent cetuximab RT will have improved 2 yr locoregional control compared to unselected patients who receive cetuximab RT ie the cetuximab RT arm in the seminal Bonner randomized trial.

16.2 Sample Size Justification

The sample size justification is based on the primary hypothesis that patients who respond to neoadjuvant cetuximab will have at least a 25% greater two-year rate of locoregional control, compared to historical data- in the seminal Bonner randomized trial, patients treated with cetuximab and radiotherapy (but completely unselected) had a 50% locoregional control rate. We feel an improvement of 25% in LRC is very reasonable given the huge difference that rash made in the Bonner trial- of those patients receiving cetuximab RT, patients who developed a significant rash had OS of 68.8 months *vs* 25.6 months for those w no or minor rash; HR 0.49, 0.34–0.72; p=0.002.

We assume patients will be accrued uniformly over three years and then followed for an additional two years past the accrual period (after the last patient's accrual). Assuming no loss to follow-up and exponentially distributed event times, we used an exponential MLE one-sided test to detect an increase in locoregional control rate from 50% to 75% for sample size calculation. It would require 16 cetuximab responders to provide 80% power to detect at least an improvement of 2 yr LRC from 50% to 75% compared to historical controls, with the use of one-sided test at the 0.05 significance level.We assume 60% of accrued patients will respond to neoadjuvant cetuximab. Therefore, a total of 27 total patients are required. A one-sided log-rank test to compare 2 yr LRC of the current study with the historical control will be performed for the primary hypothesis.

16.3 Methods for Randomization and Stratification
This is a pilot study, so there will be no randomization.

16.4 Outcome Measures
The main outcome measure is 2 yr locoregional control in cetuximab responders.

Secondary outcomes include percent of patients who progress during 3 weeks of neoadjuvant cetuximab by CT RECIST 1.1 criteria, and 2 yr locoregional control for non-responders to neoadjuvant cetuximab.

Other outomes are molecular correlates. The study is powered only for the main outcome measure. Secondary outcome measurements are descriptive.

16.5 Statistical Analysis
Most of our endpoints for this study are descriptive, and the study is only powered for the primary endpoint. We will report

1. Locoregional control at 2 years for cetuximab responders
2. Percentage of patients who progress during neoadjuvant cetuximab per RECIST 1.1 CT criteria
3. Locoregional control at 2 years for non-responders to cetuximab. We will perform preplanned subset analysis on locoregional control at 2 years for patients who are HPV + vs -.

16.6 Assumptions
The main assumption is that the population in the Bonner trial (EBRT +- cetuximab) and the population involved in this protocol are similar in susceptibility to cetuximab, so that the percentage of patients who develop cetuximab related folliculitis in response to cetuximab will be somewhat similar (it was about 60% in the Bonner trial).

The other assumption is that the percentage of HPV+ and – patients in the Bonner trial is comparable to that in this protocol. This is very difficult to judge, since in the Bonner trial they did not check HPV status. Furthermore, HPV status seems to depend to some degree on race, as African Americans appear to be more often HPV- than whites.

16.7 Compliance and Missing Data
Compliance is defined as adhering to the protocol treatment plan, follow up imaging and appointments for at least 2 years following radiation therapy.

16.8 Interim Analysis
The expected number of patients accrued over the study duration is 27. We expect the response rate is about 60%.

The early stopping rule is determined by the posterior probability of the progression rate greater than 20%. We also assume the non-informative prior on the progression rate. The stopping

would be triggered when the posterior probability of the progression rate no less than 20% is greater than 90%. The posterior distribution of the true progression rate given that k responders are observed out of the first n patients is a beta distribution with shape parameter 1+k and scale parameter 1+n-k. *The first monitoring will be done after 12 patients* and then after every subsequent patient. For example, if 4 or more patients out of the first 12 showed progression, then the trial will be stopped (The table highlights the posterior probability being greater than 90%).

n = number of patients
k = number of the responders.
Each cell contains a posterior probability that the true progression rate is greater than 20% given that k responders are observed out of the first n patients.

n\k	0	1	2	3	4	5	6	7	8
5	0.262	0.655	0.901	0.983	0.998	1.000			
10	0.086	0.322	0.617	0.839	0.95	0.988	0.998	1.000	1.000
11	0.069	0.275	0.558	0.795	0.927	0.981	0.996	0.999	1.000
12	0.055	0.234	0.502	0.747	0.901	0.970	0.993	0.999	1.000
13	0.044	0.198	0.448	0.698	0.87	0.956	0.988	0.998	1.000
14	0.035	0.167	0.398	0.648	0.836	0.939	0.982	0.996	0.999
15	0.028	0.141	0.352	0.598	0.798	0.918	0.973	0.993	0.999
16	0.023	0.118	0.31	0.549	0.758	0.894	0.962	0.989	0.997
17	0.018	0.099	0.271	0.501	0.716	0.867	0.949	0.984	0.996
18	0.014	0.083	0.237	0.455	0.673	0.837	0.932	0.977	0.993
19	0.012	0.069	0.206	0.411	0.63	0.804	0.913	0.968	0.99
20	0.009	0.058	0.179	0.37	0.586	0.769	0.891	0.957	0.986
21	0.007	0.048	0.154	0.332	0.543	0.733	0.867	0.944	0.98
22	0.006	0.04	0.133	0.297	0.501	0.695	0.84	0.928	0.973
23	0.005	0.033	0.115	0.264	0.46	0.656	0.811	0.911	0.964
24	0.004	0.027	0.098	0.234	0.421	0.617	0.78	0.891	0.953
25	0.003	0.023	0.084	0.207	0.383	0.577	0.747	0.869	0.941

Note that the prior distribution will be updated based on the number of events observed at each monitoring, and resulting posterior probability of the progression rate greater than 20% will also be updated. The PI will contact with Biometrics division to obtain the updated table after each scheduled monitoring.

17. Human Subjects

17.1 Subject Population

The study population for this protocol is advanced stage III/IV head and neck squamous cell carcinoma of the oropharynx, larynx, and hypopharynx who have not yet received any treatment for their cancer.

17.2 Potential Risks

Radiation therapy for advanced head and neck SCC is always a difficult and potentially hazardous treatment, but in turn often is curative and organ preserving (as opposed to a laryngectomy or large surgical procedure). It routinely entails the risk of fatigue, skin reaction, painful mucositis requiring PEG tube feeding, permanent dry mouth, as well as the risks associated with cisplatinum (lowered blood counts, nausea and vomiting, renal damage and ototoxicity) and cetuximab (rash). These toxicities are common to any radiation therapy patient for this disease, and at least for the radiation effects, largely unavoidable.

In this protocol we will select out the partial responders to 3 weeks of neoadjuvant cetuximab, giving these patients cetuximab EBRT and non responders cisplatinum EBRT. Therefore, those patients receiving cetuximab instead of cisplatinum will be spared the toxicity associated with cisplatinum.

The possible added danger of this protocol is that patients who are not responsive to cetuximab may have their definitive treatment with cisplatinum EBRT delayed. However, the PI recently selected 15 patients at Rutgers New Jersey Medical School - Newark (where we anticipate most of the patients will come from) and determined the time from biopsy to start of chemoRT or cetuximab RT. The average time was 6.8 wks and median 6 wks. Therefore, we anticipate that the patients on this protocol will start RT in a similar timeframe as they would if they were off protocol. In those patients who would normally have received cetuximab anyway, on this protocol they receive a 3 week loading dose instead of the usual 1 week, so receive an extra 2 weeks of cetuximab prior to RT. Again, we think that in this protocol they would likely start RT in a similar timeframe as they would off protocol.

17.3 Consent Procedures

Current FDA, OHRP, NIH, state and institutional regulations concerning informed consent will be followed. An IRB approved written informed consent document that embodies the elements of informed consent is required §46.116.

1. The investigator shall explain participation is voluntary and all aspects of the study, purpose of the study, treatment plan, procedures, risks, benefits, alternatives, and the right to refuse and withdraw at any time without penalty in lay language.

2. The investigator will answer all the patient's questions regarding the study.

3. The investigator shall give the patient adequate opportunity to read and take home to discuss with family and friends.

4. If the patient decides to participate in the study, he/she will be asked to sign the Informed Consent Document. A copy of the signed Informed Consent Document will be given to the subject and this will be documented in the patient's medical record.

5. The investigator shall inform all patients they have the right to refuse study participation and withdraw their participation at any time without penalty and will be treated without prejudice.

17.4 Non-English Speaking Patients

Where informed consent is documented in accordance with §46.117(b)(1), the written consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with a consent document written in a language understandable to them.

1. An IRB approved short form written document shall be presented in a language understandable to the subject.

2. The IRB approved English informed consent document may serve as a summary.

3. An interpreter fluent in English and the patient's language shall present the English IRB consent form offered, read it and orally present it to the patient.

4. Through the interpreter, the investigator will explain participation is voluntary and all aspects of the study, the purpose of the study, treatment plan, procedures, risks, benefits, alternatives, and the right to refuse and withdraw at any time without penalty in lay language.

5. Through the interpreter the investigator will answer any questions the patient may have.

6. The investigator shall give the subject adequate opportunity to take the IRB approved English informed consent document home for review by family and/or friends who are fluent in English and the language understandable by the patient.

7. If the patient decides to participate in the study, he/she will be asked to sign the short form document.

8. The IRB approved informed consent document will be signed by the person obtaining consent as authorized under the protocol

9. The written short form document and the English informed consent document will be signed by the witness.

10. When the person obtaining consent is assisted by a translator, the translator may serve as a witness.

11. A copy of the signed IRB approved short form document and the English informed consent document will be given to the subject and this will be documented in the patient's medical record.

12. Through the interpreter, the investigator shall inform all patients they have the right to refuse study participation and withdraw their participation at any time without penalty and will be treated without prejudice.

Regarding the photos of face and upper chest, note that these are not routine, but are done for research purposes in this protocol, as the presence/absence of folliculitis determines the chemotherapy that is received concurrently with radiation

17.5 Potential Benefits

Potential benefits to the patients and to the head and neck population is clear- if we can select out the patients who will be treated well with a high locoregional control rate with cetuximab EBRT, then those patients will be able to escape the higher toxicity associated with cisplatinum EBRT, such as increased mucositis, dysphagia and need for PEG, nausea and vomiting, pain and need for narcotic pain medication, hematologic toxicity, renal toxicity and ototoxicity. There is a potential benefit for both HPV + and – patients, as both may potentially receive less toxic therapy- perhaps even more so for the HPV + patients, as they should have a better prognosis, and may benefit from de-escalation of therapy.

17.6 Risk-Benefit Ratio

This study has a very reasonable risk benefit ratio. The standard for these advanced HNSCC patients is either cisplatinum EBRT or cetuximab EBRT, and there are no clear criteria to decide which therapy is optimal (10% OS benefit in the Bonner cetuximab RCT vs 6.5% OS benefit for concurrent chemotherapy in MACH NC meta analysis). Older patients with worse performance status often receive cetuximab EBRT due to the gentler toxicity profile. The risk is that cisplatinum EBRT is superior to cetuximab EBRT and that some patients will be treated on an inferior regimen. As it is unclear that one regimen is superior to the other, and patients are being treated off protocol on either regimen, it is difficult to assess this risk as real or not.

The benefit is that if we can select out the patients who will be treated well with a high locoregional control rate with cetuximab EBRT, then those patients will be able to escape the higher toxicity associated with cisplatinum EBRT.

17.7 Gender and Minorities

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

18. Economic/Financial Considerations

The treatment modalities of this protocol (radiation, cisplatinum, cetuximab) are standard of care and so will be paid per usual, by insurance or government agencies (charity care, medicare, Medicaid). The molecular correlates include RNA sequencing and testing for DNA mutations using FoundationOne™ (or other certified genomic analysis facility) assay. The Cancer

Institute of New Jersey (via Precision Medicine) will pay for RNA sequencing. We have been in negotiations with FoundationOne™ (or other certified genomic analysis facility) to have them perform the DNA mutation testing gratis, but as of 11/26/13, have nothing in writing-therefore we will collect the paraffin blocks (which will keep for many years) as described in the protocol, and DNA mutation testing will depend on FoundationOne™ (or other certified genomic analysis facility) doing the test for free, or PI/sub-investigators obtaining alternate funding.

19. Publication of Research Findings

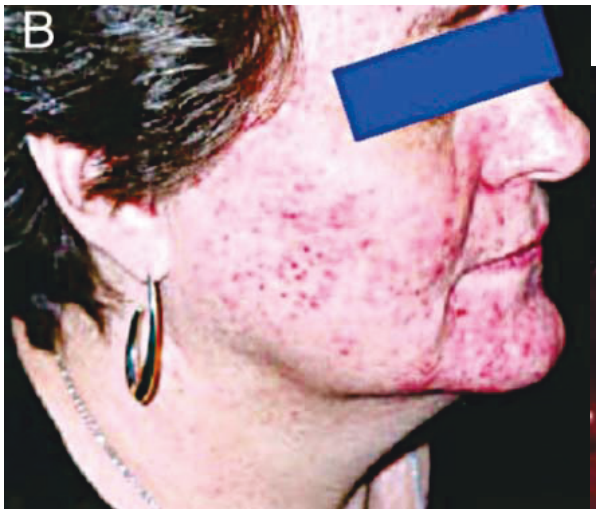
The policies and procedures of Rutgers Cancer Institute of New Jersey legal department (see: Investigator's Handbook) will govern publication of the trial. It is expected that the results of this trial will be submitted for publication in a timely manner following the conclusion. The PI, and all co-authors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

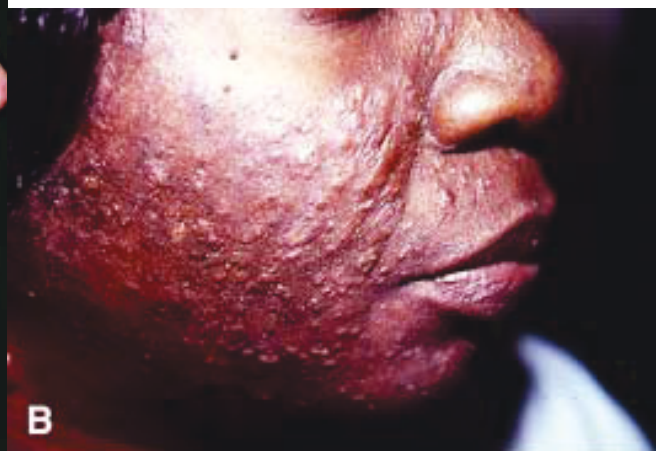
Appendix A
Performance Status Criteria

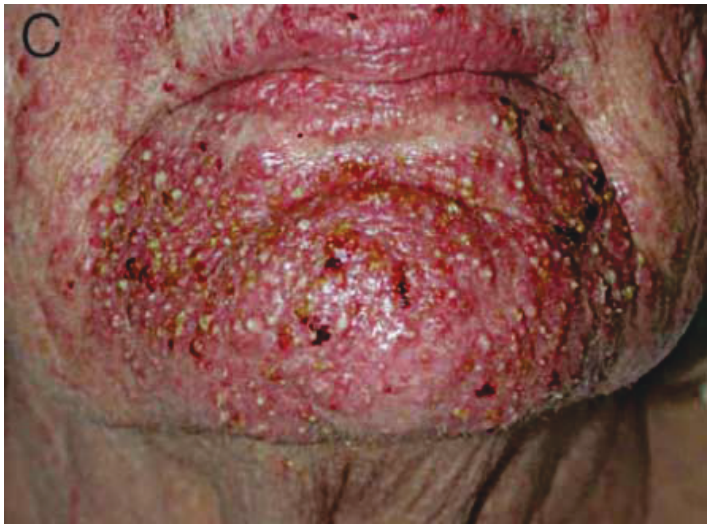
ECOG Performance Status Scale	Karnofsky Performance Scale

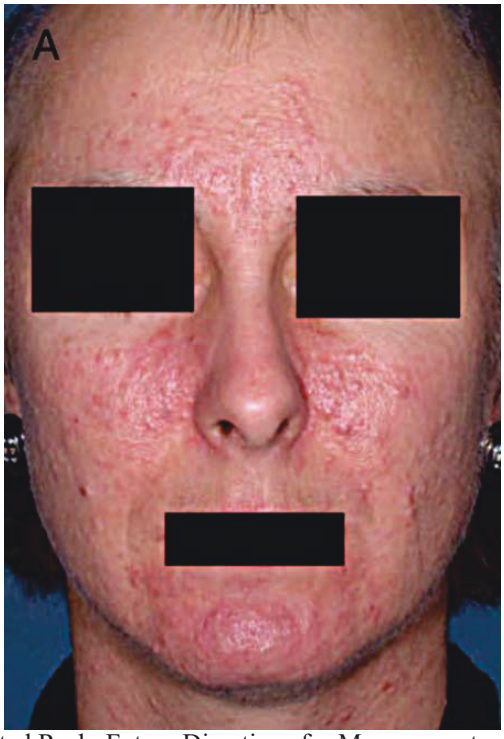
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted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

Appendix B
Examples of Cetuximab related folliculitis









Pérez-Soler R, Delord JP, Halpern A et al. HER1/EGFR Inhibitor-Associated Rash: Future Directions for Management and Investigation Outcomes from the HER1/EGFR Inhibitor Rash Management Forum. Oncologist. 2005 May;10(5):345-56.

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