LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #1
Version Date: 10/9/14

LCCC 1330: A Phase II study of weekly carboplatin, paclitaxel and cetuximab for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN)

AMENDMENT INCORPORATES:

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY

Protocol Changes:
The version date was updated throughout the protocol.

Multicenter language added to the protocol, because sites other than UNCCH will be participating in the study. (sections 7.3, 9.2, 9.3, 9.4, 9.5, 9.6 and 9.8)

Clarified that only patients who enroll at UNC will be asked to co-enroll into LCCC1108 (sections 1.6, 2.2.7, 6.0 and 6.6)

Clarified in exclusion criteria 3.2.2. that wash-out for prior radiation refers to definitive radiation therapy, not palliative radiation.
Clarified that in patients without diabetes, if glucose testing is not covered by insurance, glucose testing is not be mandated by the protocol (sections 6.0-6.3).

Added existing statement from footnote in table in section 4.4.1: Patients for whom cetuximab is discontinued due to grade 3-4 infusion reactions may complete the protocol therapy with carboplatin and paclitaxel alone, to sections 4.2 and 4.4.

Clarified in footnote to 4.4.1 table that if patient has a grade 1-2 infusion reaction during cetuximab, but is successfully rechallenged at a 50% lower infusion rate, it is acceptable to later re-increase back towards standard infusion rate

THE ATTACHED VERSION DATED October 9, 2014 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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Signature Page

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Jared Weiss, MD

PI Signature: _____

Date:_____

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is a non-randomized, open-label multicenter phase II trial of 38 patients with recurrent or metastatic SCCHN. Patients must have ECOG performance status of 0-1 with good organ function and will be treated with six weekly cycles of carboplatin, paclitaxel and cetuximab. Following assessment of response, the treating physician at their discretion may continue to treat with weekly cetuximab as maintenance until disease progression. The study is designed to evaluate whether this regimen improves median overall survival (OS) as compared to an historical control population treated with a platinum plus 5-fluorouracil (5-FU). There is currently no agreed upon first line therapy for recurrent or metastatic SCCHN; regimen options are highly toxic, inconvenient and resource intensive. Our study regimen has been used extensively for induction therapy and off-protocol in palliative care, but treatment outcomes have yet to be defined by a clinical trial.

1.2 Squamous Cell Carcinoma of the Head and Neck

The incidence of SCCHN in the United States in 2013 was estimated at 43,640 cases[1]. Patients arrive at a designation of having "incurable" head and neck cancer somewhat differently from other cancers. For example, while 75% of lung cancer patients present with metastatic disease, <10% of patients with SCCHN present with metastases. Risk factors for distant metastases include primary site (as shown in Table 1 below), nodal status, tumor size, age and race. [2]

Table 1. Risk of Metastases by Primary Tumor Site

Site	SEER (n)	Metastatic at Presentation		95% CI
		N	%	
Lip	5,975	20	0.33%	0.20-0.52%
Oral Cavity	16,385	320	1.95%	1.75-2.18%
Oropharynx	17,783	729	4.10%	3.81-4.40%
Hypopharynx	1,866	128	6.86%	5.75-8.10%
Supraglottis	8,114	270	3.33%	2.95-3.74%
Glottis	13,085	87	0.66%	0.53-0.82%
Subglottis	356	12	3.37%	1.75-5.81%
Sinus	1,068	69	6.46%	5.06-8.11%
Nasopharynx	2,610	177	6.78%	5.85-7.81%

The relevant population is unfortunately much larger, because a substantial portion of patients will eventually become incurable because of local recurrence and/or metastatic spread.

1.3 Chemotherapy for SCCHN

Typically, definitive (curative) approaches include surgery and radiotherapy and may include one or more anti-neoplastic drugs. Induction or neo-adjuvant chemotherapy is chemotherapy given prior to definitive therapy. Unlike most cancers where studies are initially performed in the metastatic setting and then extended to adjuvant use, much drug development in head/neck cancer has been studied in the induction setting, creating an opportunity for extension to the metastatic and recurrent setting.

As a consequence of high rates of early presentation, curative therapy may have been attempted one or more times prior to a shift in goals of care to non-curative therapy. When a cure is no longer possible, or when curative attempts have too low a probability of success relative to expected risks, functional deficits, or poor cosmetic results, the focus of care turns towards extension of duration of life and improvement in quality of life.

Limited data make the exact portion of patients who could benefit from palliative therapy difficult to estimate. With more than 40,000 new cases per year (25% of which will ultimately be fatal), over 13,000 patients per year in the US alone will be eligible for palliative therapy (SEER, cancer.gov). However, the rising incidence of human papillomavirus (HPV)-related oropharynx cancer and the continuing pandemic of smoking make these estimates, likely conservative. Despite this sizeable number, palliative head and neck regimens are under-studied. In the history of palliative head and neck oncology, there has been only 1 positive phase III study, the EXTREME trial.[3]

In the EXTREME trial, 442 patients with recurrent or metastatic SCCHN were assigned to a first-line regimen of platinum (cisplatin [100 mg/m^2 on day 1] or carboplatin [area under the concentration x time curve [AUC] of 5mg/mL/min for 60 minutes on day 1]) plus fluorouracil (1000 mg/m^2 per day for four days) every three weeks with or without cetuximab (400 mg/m^2 for the initial dose, followed by subsequent weekly doses of 250 mg/m^2). Chemotherapy was given for a maximum of six cycles, although patients in the cetuximab arm who had at least stable disease received weekly cetuximab maintenance monotherapy until disease progression or toxicity. Chemotherapy plus cetuximab significantly prolonged OS compared with chemotherapy alone (median 10.1 versus 7.4 months, hazard ratio for death 0.80, 95% CI 0.64-0.99). Significant improvements were also seen in median progression free survival (PFS): 5.6 versus 3.3 months and overall response (OR rates; complete response (CR) + partial response (PR)) of 36 versus 20 percent, respectively. This regimen (EXTREME) is both toxic and insufficiently effective and thus, new effective therapies have a huge potential to alleviate suffering.

No single regimen has been accepted as the standard first-line therapy in the management of locally recurrent or metastatic disease. Until the EXTREME regimen, no combination regimen demonstrated a survival advantage over any other regimen. However, most oncologists have not routinely accepted this three-medication regimen due to concerns about toxicity; 82% of the patients on the experimental arm experienced a grade 3 or 4 event. Others find the infusional 5-FU inconvenient for the typical patient in that it requires surgical implantation of a PORT and an infusion pack for four days during therapy. In addition, infusional 5-FU may cause substantial toxicity, including mucositis and diarrhea,

which can be especially problematic in nutritionally depleted patients with compromised performance status and GI integrity. The cisplatin-based regimen is also resource-intensive for the infusion room, requiring over 5 hours at UNC.

Most patients, and many oncologists, prefer less toxic regimens when cure is not the goal of care. Thus, in addition to rejecting cisplatin, other cytotoxic agents with unfavorable side effect profiles, such as 5-FU and docetaxel, are often rejected. To gain popular usage, a regimen must be both effective in extending duration of life, and associated with an acceptable toxicity profile. To this end, the most frequently used regimens in practice combine carboplatin, paclitaxel and cetuximab.

Paclitaxel is as active as 5-FU in metastatic/recurrent SCCHN, but is less toxic and more convenient for the patient. A phase III study, ECOG 1395, randomized patients with metastatic/recurrent SCCHN to cisplatin plus 5-FU or cisplatin plus paclitaxel. Survival was comparable between the two arms, but toxicity favored paclitaxel:

Grade 3-5 Toxicities (by arm) in ECOG 1395[4]

Toxicity	CF Arm (n=106)			CP Arm (n=108)		
	3 (%)	4 (%)	5 (%)	3 (%)	4 (%)	5 (%)
Leukopenia	45	18	-	27	8	-
Granulocytopenia	27	40	-	25	30	-
Thrombocytopenia	17	6	-	3	1	-
Anemia	31	2	-	9	4	-
Infection	15	2	4	8	1	4
Genitourinary	2	1	-	-	1	-
Nausea	18	1	-	17	1	-
Vomiting	11	7	-	6	4	-
Diarrhea	3	3	-	1	-	-
Stomatitis	24	7	-	-	-	-
Hemorrhage	-	1	1	-	-	1
Mucositis	1	-	-	-	-	-
Liver	1	-	-	3	-	-
Cardiac	2	-	1	2	2	-
Hypotension	2	-	-	3	2	-
Neurosensory	4	-	-	5	-	-
Neuromotor	3	-	-	4	-	-
Metabolic	11	4	-	8	2	-
Fatigue	8	1	-	4	3	-
Dehydration	3	2	-	4	-	-
Other	5	-	1	5	1	-
Worst Overall	40	50	7	33	42	5
Abbreviations: CF, cisplatin plus fluorouracil; CP, cisplatin plus paclitaxel						

A phase II study of combination paclitaxel and cetuximab demonstrated a median PFS of 4.2 months and median OS of 8.1 months. [5, 6] While carboplatin and paclitaxel have been studied in 3-week treatment cycles in patients with recurrent/metastatic SCCHN, weekly administration of these agents along with cetuximab is often utilized in clinical practice based on the favorable experience seen in the induction setting. [6, 7] [8] [9] However, this approach has never been prospectively validated in the metastatic/recurrent setting.

Kies and associates treated 47 patients with locally advanced (N2b or greater) non-metastatic disease with six weekly cycles of carboplatin AUC2, paclitaxel 135mg/m^2 and cetuximab 400mg/m^2 loading followed by 250mg/m^2 weekly. Post induction therapy, patients received radiation therapy alone (n=23), chemoradiation (n=23), or surgery alone (n=1) depending on their stage and quality of response to induction. OR at the end of radiation therapy was 96% with a CR of 70%. Of note, the subset of patients positive for HPV-16 experienced a better PFS and OS compared to those with tumors testing negative for HPV-16. The most common non-hematologic toxicity during induction therapy was rash/folliculitis (grades 2 and 3 in 38% and 45% of patients, respectively), followed by fatigue (40% grade 2 and 2% grade 3), diarrhea (9% grade 2 and 9% grade 3) and sensory neuropathy (15% grade 2 and 2% grade 3). The most common grade 2 to 4 hematologic toxicity was neutropenia (grades 2, 3, and 4 in 23%, 19%, and 2% of patients, respectively). There were no instances of febrile neutropenia. Dose reductions were needed in one patient for cetuximab and in four and two patients for paclitaxel and carboplatin, respectively. Treatment delays of ≥7 days occurred in 60% of patients.

Wanebo et al, under the aegis of the ECOG, treated operable patients with stage III or IV disease with weekly carboplatin AUC2, paclitaxel 90mg/m^2 and cetuximab 400mg/m^2 loading followed by cetuximab 250mg/m^2 weekly for six weeks. During therapy, patients underwent tumor-staging biopsies at the primary site until biopsy negativity. Forty of 67 evaluable patients had a clinical response to induction chemotherapy and 26 (65%) had a biopsy-proven CR. After 50 Gy chemoradiation (concurrent with carboplatin AUC1, paclitaxel 30mg/m^2 and cetuximab 250mg/m^2) all patients who had not yet had a negative biopsy were biopsied—all were negative. Together, the Kies and Wanebo reports provide very strong support for induction regimens that include a taxane, carboplatin, and cetuximab.

1.6 Study Rationale

Because of their high response rates and low toxicity, the taxane, carboplatin, cetuximab regimens have frequently been adapted for use in the palliative setting. At UNC, we have observed high rates of response, leading to symptomatic benefit and low toxicity. Further, the regimen de-medicalizes the patient's life in several important ways. First, unlike with the EXTREME regimen, no PORT or 4 day infusion is required. Second, the regimen gives only six weeks of cytotoxic therapy. Finally, in our experience there is a low rate of severe toxicity and this, coupled with the high rate of response, may improve quality of life. We are not aware of any presented or published results on the use of this combination in palliative therapy; with the adoption of this regimen in clinical practice, documentation of its benefit via conduct of a clinical trial is needed.

We propose a study designed to detect an improvement in median OS versus a historical control. The control arm from the EXTREME trial achieved a median OS of 7.4 months. We hypothesize that a less toxic and more effective 3-drug regimen will result in improved median OS compared with the control arm from EXTREME (median 7.4 months). The toxicity associated with EXTREME is primarily attributable to the cisplatin and 5FU cytotoxic backbone as its toxicity has been consistent in multiple studies of both palliative therapy and induction therapy. If a 4-month improvement in OS is achieved with acceptable toxicity, we will consider this regimen worth of further study.

Secondary objectives will include characterizing changes in quality of life (QoL), symptoms and toxicities. Patients at UNC only will be encouraged to co-enroll into the UNCseq protocol for further exploration of associations between genetic changes and clinical outcomes.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To estimate OS in recurrent or metastatic SCCHN after treatment with weekly carboplatin, paclitaxel and cetuximab for 6 weeks with or without the addition of maintenance weekly cetuximab

2.2 Secondary Objectives

2.2.1 To estimate OR after study treatment in recurrent or metastatic SCCHN after treatment with weekly carboplatin, paclitaxel and cetuximab for 6 weeks

2.2.2 To estimate PFS in recurrent or metastatic SCCHN patients treated with weekly carboplatin, paclitaxel and cetuximab for 6 weeks with or without the addition of maintenance weekly cetixumab

2.2.3 To characterize grade 3 and 4 toxicities associated with this regimen as assessed via clinician assessment.

2.2.4 To describe patient-reported symptoms associated with this regimen in SCCHN.

2.2.5 To evaluate the impact of weekly carboplatin, paclitaxel and cetuximab on quality of life as measured by the FACT-HN questionnaire

2.2.6 To estimate OS, PFS, and OR in HPV+ and HPV- patients separately (pre-planned subgroup analysis)

2.2.7 To explore associations between OS, PFS, and OR with genetic information acquired from co-enrollment on LCCC1108 (UNC patients only)

2.3 Primary Endpoint

2.3.1 OS is defined as the time from D1 of treatment under this protocol until death as a result of any cause.

2.4 Secondary Endpoints

2.4.1 OR, CR and PR are defined per RECIST1.1

2.4.2 PFS is defined as the time from D1 of treatment under this protocol until progression or death as a result of any cause.

2.4.3 Clinicians will use NCICTCAEv4 for grading of toxicity; patients will report symptoms via the UNCH Hematology and Oncology Outpatient Clinic Intake – Symptom Report Form (see appendix B)

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study:

3.1.1 Age ≥ 18 years old

3.1.2 Histologically or cytologically confirmed recurrent or metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- All primary sites are eligible excluding WHO type III or EBV nasopharyngeal (WHO type I and WHO type II allowed as long as they are EBV negative)

3.1.3 ECOG performance status 0-1

3.1.4 Adequate organ and marrow function as defined below. Laboratory tests should be completed within 14 days prior to registration:

- ANC ≥ 1,500/mm^3
- Platelets ≥ 100,000/mm^3
- HgB > 9g/dL (acceptable to reach this by transfusion)
- Total bilirubin ≤1.5mg/dL
- Albumin > 2.5 g/dL
- AST(SGOT)/ALT(SGPT) ≤ 2.5X institutional upper limit of normal, alkaline phosphatase ≤ 2.5 x upper limit of normal
- GFR > 30 mL/min (by standard Cockroft and Gault formula or measured via 24 hour urine collection)

3.1.5 Women of childbearing potential (WOCBP) with negative serum or urine pregnancy test within 7 days of D1 of treatment

3.1.6 WOCBP and men must agree to use adequate contraception prior to study entry and for duration of treatment under this protocol; adequate contraception is defined as any medically recommended method (or combination of methods) per standard of care.

3.1.7 Cancer must be considered incurable by the treating clinician

3.1.8 Ability to understand and willingness to sign a written informed consent document

3.2 Exclusion Criteria

Any subject meeting any of the following exclusion criteria at baseline will be excluded from study participation:

3.2.1 History of prior cumulative exposure to $\geq$ 300mg/m^2 cisplatin, AUC of 18 of carboplatin, or their combined equivalent within one year prior to enrollment

3.2.2 Surgery or definitive radiation within the four weeks prior to D1 of treatment under this protocol (there is no restriction on timing of palliative radiation)

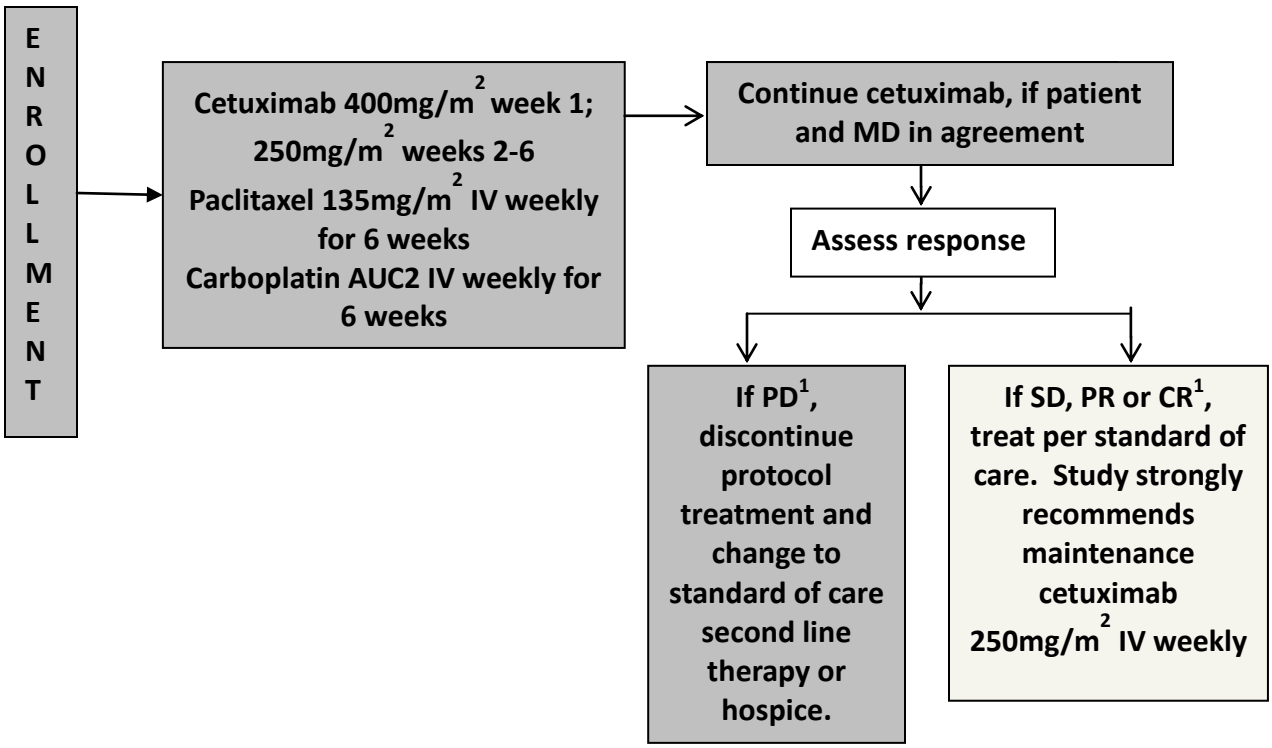
3.2.3 Prior systemic chemotherapy unless it was part of definitive-intent (curative intent) treatment more than 6 months before study entry

3.2.4 Other active, invasive malignancy requiring ongoing therapy or expected to require systemic therapy within two years; localized squamous cell carcinoma of the skin, basal-cell carcinoma of the skin, carcinoma in-situ of the cervix, or other malignancies requiring locally ablative therapy only will not result in exclusion

3.2.5 Pregnant or lactating female

4.0 TREATMENT PLAN

4.1 Schema



[1]PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response. See section 6.7.3 for more details.

A 6-week course of weekly carboplatin, paclitaxel and cetuximab at the doses outlined in the above schema will be administered to 38 patients with recurrent or metastatic SCCHN. Once protocol therapy is complete, cetuximab may be continued if patient and physician agree. Within 3 weeks of end of protocol therapy, response will be assessed, and if the patient has achieved at least stable disease (SD), the treating physician at their discretion may continue to treat with weekly cetuximab as maintenance until progression. Imaging during maintenance will be repeated at the discretion of treating physician, with a suggested schedule of every 6-9 weeks.

4.2 Treatment Dosage and Administration

See section 5.0 for more detailed information on individual drugs, including recommended hydration and associated toxicities.

Drug	Dose and Route	Infusion Duration	Schedule
Cetuximab	400mg/m^2 IV loading dose	120 min	Day 1 week 1[a]
	250mg/m^2 IV maintenance dose	60 min	Day 1 weeks 2-6[b]
Paclitaxel[c]	135mg/m^2 IV (post cetuximab)	30 min	Day 1 weeks 1-6[a]
Carboplatin[c]	AUC2 IV (post paclitaxel)	30 min	Day 1 weeks 1-6[a]

[a] Each week of chemotherapy is considered one cycle of therapy.
[b] Cetuximab may be continued weekly at the discretion of the investigator provided the patient has achieved at least SD at the time of first tumor imaging
c Patients for whom cetuximab is discontinued due to grade 3-4 infusion reactions may complete the protocol therapy with carboplatin and paclitaxel alone.

4.2.1 Cetuximab

While in clinic, patients should receive 0.9% Sodium Chloride at 100 mL/hr, or per institutional standard. The first infusion of cetuximab (day 1 week 1) will be administered at 400mg/m^2 and infused over 120 minutes (maximum infusion rate of 10mg/min). Subsequent weekly infusions (day 1 of weeks 2-6) of cetuximab will be dosed at 250mg/m^2 and infused over 60 minutes (maximum infusion rate of 10mg/min). Actual body weight will be used to calculate dose, and cetuximab should be administered with the use of a low protein binding 0.22-micrometer in-line filter. Monitor patients for 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen).

Please see section 4.2.4 for important information on premedications and monitoring during administration, and section 4.4.1 for adjustments in infusion if patient experiences infusion-related reactions.

4.2.2 Paclitaxel

Paclitaxel 135mg/m^2 will be infused over 30 minutes. Paclitaxel should be infused before carboplatin. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Actual body weight will be used for the calculation. On the day treatment with paclitaxel is due, if patient weight has changed by >10%, recalculate the body surface area and dose of paclitaxel.

4.2.3 Carboplatin

Carboplatin will be infused at an AUC of 2, with the dose calculated using the Calvert equation (total dose (mg) = (target AUC) x (GFR +25). The dose will be re-calculated *prior to every cycle* in order to adjust for any potential change in renal function as assessed via serum creatinine (also checked each cycle). The patient's glomerular filtration rate (GFR) as creatinine clearance (CrCL) in mL/min will be calculated using the Cockcraft-Gault formula, with weight defined as actual body weight:

For males: Creatinine clearance (GFR) (mL/min) = $\frac{(140 - \text{age}) \times \text{weight in kilograms}}{72 \times \text{serum creatinine in mg/dl}}$

For females: use same formula but multiply by 0.85 for creatinine clearance

A maximum GFR of 125 mL/min will be used. Therefore, the maximum dose of carboplatin possible in this study will be 300 mg. The carboplatin will be infused over 30 minutes. Carboplatin should be administered after paclitaxel.

4.2.4 Premedications

Cetuximab

As discussed in the adverse events section (see section 5.1.4), the rate of infusion reaction to cetuximab is much higher in the Southeast than other areas of the country. Therefore, at UNC the following procedures will be recommended during the administration of cetuximab:

- Premedicate all cetuximab infusions with diphenhydramine 50 mg PO or IV (may be reduced to 25mg at treating clinician discretion) and dexamethasone 8-20 mg PO or IV.
- Administer an H2 blocker (e.g. cimetidine) PO or IV.
- Patient to be observed one-on-one with first treatment. Physician, physician's assistant (PA), or nurse practitioner (NP) must be present at initiation and through at least the first 15 minutes of first infusion.
- Discontinue cetuximab for bronchospasm and/or anaphylaxis.
- Have available at bedside: O2, epinephrine for subcutaneous administration (1:1000, 0.3mg) and methylprednisolone 125 mg IV. Administer epinephrine SQ immediately at the first sign of possible anaphylaxis as physician is being notified. Administer methylprednisolone 125 mg IV for symptomatic anaphylactoid reactions (rash, hives, wheezing, light headedness) with hypotension.

Paclitaxel and Carboplatin
Premedications will not be mandated by protocol, but provided per institutional guidelines. Standard recommendations include oral ondansetron 24mg PO (or 8mg IV), oral cimetidine 300mg (or other H2 blocker) and oral dexamethasone 10mg; but these are not mandatory. Prophylactic aprepitant will not be recommended, but will be allowed both in the primary prophylactic and in the secondary prophylactic setting.

Other regimens may be optimal for the care of individual patients.

4.3 Supportive Care Guidelines

4.3.1 Anti-emetic Medications

Section 4.2.4 includes recommendations for primary prophylactic anti-emetic regimens for carboplatin and paclitaxel chemotherapy. The study further recommends, but does not mandate, that all patients be provided with a prescription for ondansetron 8mg to be used every 8 hours as needed during the first three days following any given treatment and prochlorperazine 10mg to be used every 6 hours as needed during subsequent days. Optimal supportive care involves adjustment of antiemetic medications by experienced practitioners and the study endorses such adjustment as needed. Other medications frequently helpful for the treatment of chemotherapy-induced nausea and vomiting include metoclopramide, lorazepam, diphenhydramine, steroids, and olanzapine.

4.3.2 Growth factors

Use of erythropoietin stimulating agents (ESAs) will not be permitted during chemotherapy. The use of prophylactic filgrastim (G-CSF) during induction chemotherapy may be considered (see table in section 4.4.2). Peg-filgrastim (Neulasta®) is not permitted. The use of filgrastim will be permitted at the discretion of the treating physician in patients with low blood counts that threaten treatment continuity. Filgrastim administration is strongly advised in patients who have previous febrile neutropenia or who have treatment delays due to neutropenia. When filgrastim is used, it should be administered per investigator/institution's standard of care. The number of days of filgrastim is up to the discretion of the treating MD; however, to protect patient safety, the patient must start at least 24 hours after the dose of chemotherapy and stop at least 48 hours prior to the next dose. The dose of the filgrastim can be adjusted based on the investigator's discretion.

4.4 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives any treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity. Patients for whom cetuximab is discontinued due to grade 1-2 infusion reactions may complete the protocol therapy with carboplatin and paclitaxel alone.

4.4.1 Dose delays and dose modifications of cetuximab for toxicity

Dose adjustments are based on highest grade toxicity occurring any time during each weekly cycle:

Toxicity	Cetuximab Modification for Subsequent Administration
Infusion Reaction	
Grade 1-2	Reduce infusion rate by 50%[3]
Grade 3-4	Permanently discontinue cetuximab[1]
Acneform rash	
≤Grade 2	Maintain dose
≥Grade 3 first occurrence	Hold cetuximab for 1-2 weeks then resume at full dose
≥Grade 3 repeat occurrence	Hold cetuximab for 1-2 weeks then resume at reduced dose[2]

[1]Permanent discontinuation is consistent with guidelines and standard of care in Southeastern United States. Patients for whom cetuximab is discontinued due to grade 3-4 infusion reactions may complete the protocol therapy with carboplatin and paclitaxel alone.
[2]After the second occurrence of grade 3-4 acneform rash, cetuximab will be held 1-2 weeks, until it has improved to < grade 3. For the second occurrence of grade 3-4 acneform rash, cetuximab will be restarted at 200mg/m^2. For the third occurrence of grade 3-4 acneform rash, cetuximab will be restarted at 150mg/m^2. During weeks when cetuximab is held, carboplatin and paclitaxel chemotherapy will continue.
[3] If successfully rechallenged at this lower infusion rate, it is acceptable to later re-increase back towards standard infusion rate

4.4.2 Suggested dose delays and dose modifications for paclitaxel and carboplatin

For AEs that require dose reductions of paclitaxel or carboplatin, please refer to the dose levels in the following table:

Dose Level	Paclitaxel (mg/m^2)	Carboplatin (AUC)
0 (starting dose)	135	2
-1	100	1.7
-2	80	1.4

Both carboplatin and paclitaxel are FDA approved chemotherapy agents that are routinely dose-adjusted by oncologists outside of protocol settings. Given the high level of clinical experience with these medications, clinicians can better individualize dose-reductions than rigid guidelines. Therefore, when dose adjustment is required, the treating clinician shall decide whether to dose-reduce one or both agents; adjustments in the table above are suggested. **Suggested** dose delays and modifications for specific toxicities are made in the table below.

	Toxicity on treatment days	**Dose Level for Subsequent Administration**	
If ANC <1, hold [2] treatment for that day. Resume the following week with the next dose (held dose is delayed, not missed). Resume per table when next dose is due if ANC ≥1	**Neutropenia[1]**	**Paclitaxel**	**Carboplatin**
	Grade 2 w/o fever (ANC <1500/mm^3 to 1,000/mm^3	Maintain dose[4]; consider G-CSF	Maintain dose[4]; consider G-CSF
	Grade 3 w/o fever (ANC <1000/mm^3 to 500/mm^3	↓1 dose level; strongly consider G-CSF	↓1 dose level; strongly consider G-CSF
	Grade 4 neutropenia (ANC <500/mm^3 or Febrile neutropenia[3])	↓2 dose levels; strongly consider G-CSF	↓2 dose levels; strongly consider G-CSF
If platelets <75K, hold [2] treatment for that day. Resume the following week with the next dose (held dose is delayed, not missed). Resume per table when next dose is due if platelets ≥75K	**Thrombocytopenia**	**Paclitaxel**	**Carboplatin**
	≤Grade 1	Maintain dose	Maintain dose
	Grade 2 (Plt 50,000-74,999)	Hold dose then ↓1 dose level	Hold dose then ↓1 dose level
	≥Grade 3 (<50,000)	Hold dose then ↓2 dose levels	Hold dose then↓2 dose levels
If Hgb<8 g/dL, transfuse PRBCs. Once Hgb is ≥ 8, therapy may resume.	**Anemia**	**Paclitaxel**	**Carboplatin**
	≥Grade 2 (Hgb <10)	Transfusion may be used as needed to maintain Hgb. If contraindicated or inadequate ↓1 dose level will be permitted but not required for Hgb<8	↓1 dose level will be permitted but not required for Hgb<8.
If ≥ grade 3, hold[2] treatment for that day. Resume per table when next dose is due if ≤grade 1	**Sensory neuropathy**	**Paclitaxel**	**Carboplatin**
	≤Grade 2	↓1 dose level	Maintain dose
	Grade 3	↓2 dose levels	↓1 dose level
	Grade 4	↓2 dose levels	↓2 dose levels

[1]Filgrastim may be used for ANC<1500 at the investigator's discretion provided they are not substituted for a required dose reduction. See section 4.3.2 for instructions on dose and duration; peg-filgrastim (Neulasta®) is NOT permitted)
[2]Hold offending agent(s) as identified in table. If have to hold > 2 weeks, discontinue agent(s)
[3] Febrile neutropenia is typically treated with hospital admission and IV antibiotics, but low risk cases may be treated on an outpatient basis.
In the event of treatment delays, patients will be treated to a total six doses of combined therapy.

	Toxicity on treatment days	**Dose Level for Subsequent Administration**	
If bilirubin >2mg/dL, hold [1] treatment for that day. Resume per table when next dose is due if bilirubin <2mg/dL	**Hyperbilirubinemia**	**Paclitaxel**	**Carboplatin**
	≤Grade 2	Maintain dose	Maintain dose
	≥Grade 3	↓1 dose level	↓1 dose level
If transaminases ≥3 x ULN hold [1] treatment for that day. Resume per table when next dose is due if transaminases < 3 x ULN	**Transaminase elevation**	**Paclitaxel**	**Carboplatin**
	Grade 1	Maintain dose	Maintain dose
	Grade 2	↓1 dose level	Maintain dose
	≥Grade 3	↓2 dose levels	↓1 dose level
If SCr >2 mg/dL, hold[1] treatment for that day. Resume per table when next dose is due if SCr<2 mg/dL	**Renal toxicity**	**Paclitaxel**	**Carboplatin**
	≤Grade 2	Maintain dose	Maintain dose
	≥Grade 3	↓1 dose level	Maintain dose
Hold[1] dose of suspected offending agent(s) until toxicity resolves to ≤Grade 1, then resume treatment with dose adjusted per table.	**Other non-specified[4]**	**Paclitaxel**	**Carboplatin**
	≥ Grade 3	↓1 dose level	↓1 dose level
[1]Hold offending agent(s) as identified in table. If have to hold > 2 weeks, discontinue agent(s)			

4.5 Duration of Protocol-directed Therapy

In the absence of treatment delays due to adverse events, treatment may continue at the discretion of the investigator for 6 cycles unless:

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

4.6 Duration of Follow Up

Patients will be followed for PFS and OS through chart review until they are lost to follow up, die or three years has passed since patient completed protocol therapy.

4.7 Removal of Patients from Protocol Therapy

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.5 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.8 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

5.0 DRUG INFORMATION

5.1 Cetuximab (Erbitux®)

Please refer to cetuximab prescribing information revised in August, 2013 (see http://packageinserts.bms.com/pi/pi_erbitux.pdf) for detailed information.

5.1.1 Supplier/How Supplied

Commercial supplies of cetuximab will be used for this study. It is available at a concentration of 2mg/mL as a 100mg/50mL single-use vial or as a 200 mg/100mL single use vial.

5.1.2 Dose and Schedule (see section 4.2)

5.1.3 Adverse Events Associated With Cetuximab

The most common adverse reactions with cetuxumab (incidence ≥25%) are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. The most serious adverse reactions with cetuximab are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure,

interstitial lung disease, and pulmonary embolus. Particular warnings and precautions (described in more detail in the prescribing information) associated with cetuximab include the following:

Infusion Reactions
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. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines, usually within minutes of starting the infusion. Infusion reactions have been reported to occur at a higher incidence in patients from the Southeastern part of the United States, including at least North Carolina and Tennessee. The overall rate of grade 3 to 4 hypersensitivity reactions during the first dose in a dataset of 88 patients treated within clinical trials, and 55 treated outside of clinical trials was 22% [10].

Cardiopulmonary Arrest
Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone in a randomized, controlled trial in patients with SCCHN.

Pulmonary Toxicity
Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving cetuximab in clinical trials.

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

Hypomagnesemia and Electrolyte Abnormalities
In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients (199/365) receiving cetuximab and was severe (NCI CTC Grades 3 and 4) in 6–17%. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of cetuximab.

5.2 Paclitaxel (Taxol®)

Please refer to paclitaxel prescribing information (April 2011) (http://packageinserts.bms.com/pi/pi_taxol.pdf) for complete information.

5.2.1 Supplier/How Supplied

Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Commercially available supplies will be used for this study.

5.2.2 Preparation and Administration

Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Procedures for proper handling and disposal of anticancer drugs should be considered. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing paclitaxel. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

Paclitaxel will be infused intravenously over 30 minutes prior to carboplatin. Actual body weight will be used for the calculation.

5.2.3 Dose and Schedule (see section 4.2)

5.2.4 Adverse Events Associated With Paclitaxel

Some of the adverse events expected with paclitaxel treatment are listed below.

Hematologic: Hematologic side effects including bone marrow suppression have been the major dose-limiting toxicity. Neutropenia less than 2,000cells/mm^3 (90%) is the most important hematological toxicity. Neutropenia was both dose and schedule dependent, and was generally rapidly reversible. The onset of neutropenia generally occurs after 8 to 10 days and recovery generally occurs after 15 to 21 days. Leukopenia less than 4,000 cells/mm^3 (90%) and less than 1,000 cells/mm^3 (17%), thrombocytopenia less than 100,000 cells/mm^3 (20%) and less than 50,000 cells/mm^3 (7%), and anemia less than 11 g/dl (78%) and less than 8 g/dl (16%) have been reported. Infections (30%), bleeding (14%), red cell transfusions (25%) and platelet transfusions (2%) have been reported.

Allergic reactions: Hypersensitivity side effects were observed in 41% of all study patients; severe reactions (2%) have been reported. The most frequent symptoms observed during the severe reactions were dyspnea, flushing, chest pain and tachycardia. Minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%), and hypertension (1%). These reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Cardiovascular: Hypotension during infusion occurred in 12% of all patients and in 3% of all courses administered. Significant cardiovascular events possibly related to paclitaxel occurred in approximately 1% of all patients. Abnormal ECG readings have been reported in 23% of all patients receiving paclitaxel and in 14% of the patients with normal baseline ECGs. The most frequently reported ECG modifications were nonspecific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats.

Neurologic: Nervous system side effects including neurotoxicity, primarily including peripheral neurosensory manifestations (60%), have generally been mild to moderate in severity. However, severe symptoms (3%) have also been reported. Other serious neurologic events (<1%) have been reported including grand mal seizures, syncope, ataxia, neuroencephalopathy and autonomic neuropathy resulting in paralytic ileus.

The frequency and severity of neurologic manifestations have been dose dependent and cumulative.

Gastrointestinal: Gastrointestinal side effects including nausea and vomiting (52%), diarrhea (38%) and mucositis (31%) have been reported. Intestinal obstruction, intestinal perforation and ischemic colitis have been reported rarely. Three cases of pancreatitis have also been reported. Gastrointestinal effects can generally be treated with standard antiemetic antidiarrheal therapy and dietary changes.

Hepatic toxicity: Hepatic side effects including elevations in bilirubin (7%), alkaline phosphatase (22%) and AST (SGOT) (19%) have been reported in patients with normal baseline levels. Hepatic necrosis and hepatic encephalopathy leading to death have been reported rarely.

Other: Musculoskeletal side effects including myalgia and/or arthralgia (60%), including severe symptoms (8%) have been reported. Nausea/vomiting, diarrhea, and mucositis were reported by 52%, 38% and 31% of all patients, respectively.

5.3 Carboplatin (Paraplatin®)

Please refer to carboplatin prescribing information (see (http://packageinserts.bms.com/pi/pi_paraplatin.pdf for detailed information). Last update is July 2010.

5.3.1 Supplier/How Supplied

Carboplatin is available as an aqueous solution for injection in single-dose vials containing 50mg, 150 mg, 450 mg, or 600 mg for administration by intravenous infusion. Commercially available supplies will be used for this study.

5.3.2 Preparation, Hydration and Administration

The appropriate dose of carboplatin aqueous solution should be further diluted per institutional guidelines. While in clinic, patients should receive 0.9% Sodium Chloride at

100 mL/hr, or per institutional standard. The carboplatin infusion should start after the completion of paclitaxel, and should be infused over 30 minutes.

5.3.3 Dose and Schedule (see section 4.2)

5.3.4 Adverse Events Associated With Carboplatin

Incidence rates of adverse events associated with carboplatin are provided in the product Prescribing Information (see http://packageinserts.bms.com/pi/pi_paraplatin.pdf). Some of the adverse events expected with carboplatin treatment are listed below.

Hematologic: Myelosuppression is dose-dependent and the major dose-limiting toxicity. Thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of patients; neutropenia with granulocyte counts below 1,000/mm^3 occurs in 16% of the patients; and leukopenia with WBC counts below 2,000/mm^3 occurs in 15% of patients. By Day 28, thrombocytopenia, neutropenia, leukopenia, typically resolve in patients receiving single-agent carboplatin. Anemia is common: 71% of patients who started therapy with a baseline above 11g/dL experienced anemia.

Allergic reactions: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely anaphylaxis with bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Neurologic: Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.

Gastrointestinal: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea (6%), constipation (6%), and gastrointestinal pain (17%).

Hepatic toxicity: Elevated alkaline phosphatase, total bilirubin, and AST have been observed.

Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

6.0 EVALUATIONS AND ASSESSMENTS

Procedure	Screening[1]/ Baseline	Day 1 (+/- 1 day) of every weekly cycle for 6 weeks[2]	Post protocol directed therapy prior to response assessment	Post-therapy assessment [3] (3 weeks after carboplatin and paclitaxel completed)	First follow-up[4]	Chart review of subsequent follow up
Study Eligibility	X					
Informed Consent	X					
Document HPV status	X					
Medical History	X[5]					
Urine or serum pregnancy (if applicable)	X[6]					
Physical Exam	X[7]	X		X	X	
ECOG Performance Status[8]	X	X		X	X	
Weight	X	X[2]		X	X	
CBC w/differential	X	X		X		
Serum chemistries[9]	X	X		X		
Calculated CrCl	X	X[10]				
Liver function tests[11]	X	X		X		
Radiographic tumor evaluation[12]	X			X	X	X
QOL (FACT-HN)[13]	X			X	X	
UNCH symptom report form	X	X		X	X	
Toxicity assessment	X	X		X[14]	X	
Carboplatin		X[2]				
Paclitaxel		X[2]				
Cetuximab		X[2]	X[15]	X[16]		
Co-enrollment into LCCC1108	X[17]					
Survival assessment					X	X[4]

End of protocol-directed therapy

Key to Time and Events Table

[1]Unless otherwise noted, screening evaluations to take place within 2 weeks prior to day 1 of study treatment. For D1 of week 1, if screening (baseline) evaluations were performed within 7 days of D1 of treatment, these do not need to be repeated.

[2]Paclitaxel, cetuximab and carboplatin administered weekly for 6 weeks.

[3]This clinic visit should take place 3 weeks (+/-1 week) after patient completes carboplatin/paclitaxel treatment or ceases therapy for other reasons (including early discontinuation)

[4]First follow-up should take place in clinic 8-12 weeks post end of therapy visit. Follow-up data for survival will be abstracted from the medical record for up to 3 years post study completion or death, whichever occurs first. Patients who come off study therapy for reasons other than progression will have their records abstracted for 3 years. Date of progression of disease will be abstracted if available. The interval of follow up will be per the standard of care practice of the treating clinician.

[5]Complete medical history at baseline to include demographics, HPV status and smoking history

[6]To be done within 7 days prior to day 1 of treatment in women of childbearing potential

[7] Physical examination to include height at baseline only, and complete examination of head and neck

[8]See Appendix A

[9]Serum chemistries to include sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, calcium, magnesium, total protein, albumin. Each time serum chemistries are scheduled, it is recommended to also check for serum glucose for all patients. However, for patients without diabetes, if glucose testing is not covered by insurance, glucose testing will not be mandated by the protocol.

[10]See section 4.2.3.

[11]Liver function tests (total bilirubin, alkaline phosphatase, AST, ALT)

[12]When possible, the same method of evaluation should be used throughout study and may include CT or MRI of the neck, and chest imaging (x-ray or CT scan at discretion of physician). CT of the neck should have IV contrast unless contraindicated (allergy or adverse reaction or renal issues). Screening radiologic evaluation may take place within 4 weeks of treatment initiation.

[13]Can be printed from Oncore

[14]Patients who have an ongoing Grade 4 toxicity at the time of discontinuation from treatment will continue to be followed until the event is resolved or deemed irreversible by the investigator.

[15] It is recommended that cetuximab be continued as maintenance therapy weekly until response assessed.

[16] In patients who achieve at least SD, recommend continuing cetuximab until disease progression. For weight change >10% (carboplatin, paclitaxel and cetuximab) or GFR change >10% (relevant to carboplatin only) it is recommended to recalculate dose.

[17] Only patients enrolled at UNC will be asked to participate in LCCC1108 (see section 6.6).

6.1 Pre-Study Assessments

Screening evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done within 4 weeks prior to the start of therapy. Pre-study (baseline) assessments include:

- Document HPV status (Note that a defined HPV status is not a requirement for entry to the study, but should be recorded when available).
- Urine or serum pregnancy test in women of childbearing potential (Note: pregnancy test to be done within 7 days of day 1 of treatment)
- Complete medical history and physical examination (including height and smoking status).
- ECOG Performance Status (see appendix A) and FACT-HN.
- Weight
- Laboratory evaluations: CBC with differential; serum chemistries (sodium, potassium, chloride, bicarbonate, magnesium, BUN, serum creatinine, calcium, liver function tests (LFTs; total bilirubin, alkaline phosphatase, AST, ALT), total protein, albumin. Each time serum chemistries are scheduled, it is recommended to also check for serum glucose for all patients. However, for patients without diabetes, if glucose testing is not covered by insurance, glucose testing will not be mandated by the protocol.
- Calculated creatinine clearance (based on Cockroft Gault, see section 4.2.3)
- Tumor evaluation: CT or MRI Scan of the neck, results from physical examination head and neck, and chest imaging (x-ray or CT scan at discretion of physician).
- Toxicity evaluation (for notation of any baseline toxicity). This includes CTCAE and collection of patient reported symptoms (via the UNCH Hematology Oncology Outpatient Symptom Report Form, see appendix B).

6.2 Treatment Assessments

Weekly assessments during carboplatin/paclitaxel chemotherapy include:

- Physical examination.
- ECOG Performance Status (see appendix A)
- Body weight
- Calculated creatinine clearance (based on Cockroft Gault, see section 4.2.3)
- Laboratory evaluations: CBC with differential; serum chemistries (see note regarding glucose in section 6.1), total protein, and albumin; LFTs
- Toxicity assessment: record any non-serious and serious AEs and assign appropriate toxicity grade (NCI CTCAE, Version 4.)
- Collect patient reported symptoms via the UNCH Hematology Oncology Outpatient Symptom Report Form

6.3 End of Treatment Assessments

(3 (+/- 1) weeks after conclusion of carboplatin/paclitaxel chemotherapy):

- Physical examination
- ECOG Performance Status (see appendix A) and FACT-HN.
- Weight
- Laboratory evaluations: CBC with differential; serum chemistries (see note regarding serum glucose in section 6.1), total protein, and albumin; LFTs
- Tumor evaluation — CT or MRI Scan of the neck, chest imaging (x-ray or CT scan at discretion of physician) and physical examination.
- Toxicity assessment: record any non-serious and serious AEs and assign appropriate toxicity grade (NCI CTCAE, version 4).
- Patient reported symptoms via the UNCH Hematology Oncology Symptom Report Form

6.4 Early Treatment Termination

The following assessments will be performed, if possible, when a subject is withdrawn from study therapy for any reason prior to completion of protocol therapy:

- Physical examination.
- Weight
- Laboratory evaluations: CBC with differential; serum chemistries, total protein, and albumin, LFTs
- ECOG Performance Status (see appendix A) and FACT-HN
- Tumor evaluation — CT or MRI Scan and physical examination.
- Toxicity assessment: record any non-serious and serious AEs and assign appropriate toxicity grade (NCI CTCAE, Version 4). Patients who have an ongoing Grade 4 toxicity at the time of discontinuation from treatment will continue to be followed until the event is resolved or deemed irreversible by the investigator.
- Patient reported symptoms via the UNCH Hematology Oncology Symptom Report Form

6.5 Follow-up Assessments

Patients who withdraw consent from study drug treatment should enter the follow-up period (unless consent to follow-up is specifically withdrawn).

Subjects will be followed every 3-6 months per standard of care, and at the discretion of the treating physician for at least 3 years following completion or termination of protocol therapy (see section 4.5), or death, whichever occurs first. Follow-up may be conducted via telephone. Follow-up assessments will focus on survival status and status of disease if known.

If tumor assessments are available for patients who have not yet experienced PD, enter the follow-up tumor evaluations in the eCRF until PD is confirmed.

6.6 Correlative Studies Procedures

HPV status is determined via IHC per standard of care. This will be documented in the eCRF.

At the time of consent, all subjects enrolled at UNC with adequate tissue will be strongly encouraged to participate in the LCCC1108 (UNCseq) study which conducts multiplex next-generation sequencing. We intend to use data from patients who also consent to LCCC1108 for pre-specified biocorrelative analyses.

6.7 Assessment of Safety

Any patient who receives treatment on this protocol will be evaluable for toxicity through the use of the NCI CTCAE v4. Further information on this assessment is provided in the time and events table.

Toxicities associated with this regimen will also be characterized through collection of patient reported symptoms via the UNCH Hematology Oncology Outpatient Symptom Report Form. See appendix B.

6.8 Assessment of Efficacy

All patients who have received at least one full cycle of treatment will be evaluable for assessment of the primary objective of OS. All patients with measurable disease who have received at least two full cycles of treatment will be evaluable for assessment of RR.

6.8.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- ≥10mm by CT or MRI scan (CT scan slice thickness no greater than 5 mm)
- 20 mm by chest x-ray.
- Clinically palpable lesions will be considered measurable if they are both at least 1cm in maximal dimension and felt by the clinician to be sufficiently accessible as to allow repeat reliable measurement with calipers.
- Clinically evident lesions on fiberoptic NPL will be considered measurable if they are both at least 1cm in maximal dimension and felt by the clinician to be sufficiently accessible and visible to allow repeat visual examination.

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

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended when contributory.

6.8.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent", or in rare cases "unequivocal progression."

6.8.3 Evaluation of Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all target lesions. Any pathological lymph node (LN) target or no must have decreased in short axis to <10mm.

Partial response (PR)−At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline 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 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)−Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

6.8.4 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR) −Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

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

Progressive disease (PD) −Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

6.8.5 Evaluation of Overall Response using RECIST 1.1 Criteria

The overall response is the response recorded from pretreatment to imaging conducted two weeks following completion of induction chemotherapy. The clinical overall response will be defined according to the following table:

Target lesions	Non-Target Lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Best overall response following chemotherapy will be ascertained by comparing pretreatment imaging with imaging following completion or early discontinuation of induction chemotherapy. Of note, imaging can be insensitive for complete response in head and neck cancer.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom,

or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered <u>unexpected if</u> the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered <u>serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes</u>:

- Death;

- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

7.3.2 Documentation and Notification

These events (SAEs or Serious SARs) must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. For Affiliate sites, an email must also be sent to the UNCCN Project Manager indicating that an SAE

or Serious SAR has been entered into Oncore (email contact will be provided at study start-up).

7.3.3 Reporting

IRB Reporting Requirements:

UNC:

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.
- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3 within 7 days of the Investigator becoming aware of the problem.

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNCCN Project Manager using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 28 days of the subject's last dose of study should be recorded as SAEs. The patient is to be discontinued immediately from the study. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

7.4 Data Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, but at least monthly, which will include the investigators as well as protocol nurses, clinical

research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, and data collection.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annual) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Endpoints

This is a single-arm phase II trial in patients with recurrent or metastatic SCCHN receiving carboplatin, paclitaxel and cetuximab. The primary endpoint of this trial is OS and secondary objectives will include overall response rate, defined as CR+PR; PFS; characterizing toxicities from the patient and physician perspective, and documenting quality of life measures.

8.2 Sample Size and Accrual

In the EXTREME study, a platinum plus 5-FU was compared to the same doublet with the addition of cetuximab; survival was improved from 7.4 to 10.1 months in the cetuximab arm. We seek to improve survival from the control arm of EXTREME (7.4 months) by 4 months to 11.4 months.

The sample size for this trial is based on testing the null hypothesis that the median PFS is 7.4 against a one-sided alternative (assuming an exponential distribution). With a one-sided test, accrual over 20 months, follow up of 18 months, and alpha of .05, 38 subjects will be required for a power of 80% (One Sample Survival; swogstat.org).

We expect to accrue 2 patients per month, reaching 38 patients in approximately 20 months.

8.3 Data Analysis Plans

The Kaplan-Meier method will be used to estimate OS and PFS, and median times will be reported with 95% confidence intervals. OR (CR+PR) after six cycles of combined chemotherapy will be reported with exact 95% confidence intervals. Descriptive statistics will be used to characterize the safety profile of the combined chemotherapy regimen and report on quality of life as measured by the FACT-HN and patient-reported symptom scores as measured by the UNCH Hematology Oncology Symptom Report Form.

As sample size permits, exploratory subgroup analyses will be performed to compare key measures of treatment efficacy (OR, OS, PFS) between HPV+/- patients, and patients with different expression of genetic markers (as gathered in LCCC1108) using appropriate non-parametric tests (Fisher's Exact, Wilcoxon Rank Sum) and the Kaplan-Meier method and Cox regression.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list

- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the CPO at the University of North Carolina before enrollment to study. For UNC patients, prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator.

For Affiliate patients, to register and confirm patient eligibility, please fax registration forms, informed consent, and source documents to 919-966-4300...

9.4 Data Management and Monitoring

The CPO UNCCN of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). UNC CPO Data Quality personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six months.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

<u>For Institutions Relying on UNC's IRB:</u>
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

9.5.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

For Institutions Relying on Their Own IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the participating institution's IRB, per its policy. Please forward the IRB response to the UNCCN Regulatory Associate by facsimile or via email within 10 business days after the original submission.

9.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:

Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.
For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:
UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

Affiliate Sites:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must also be reported to the UNCCN Project Manager. The UNCCN Project Manager will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.
For Institutions Relying on Their Own IRB:
Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNCCN Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 **REFERENCES**

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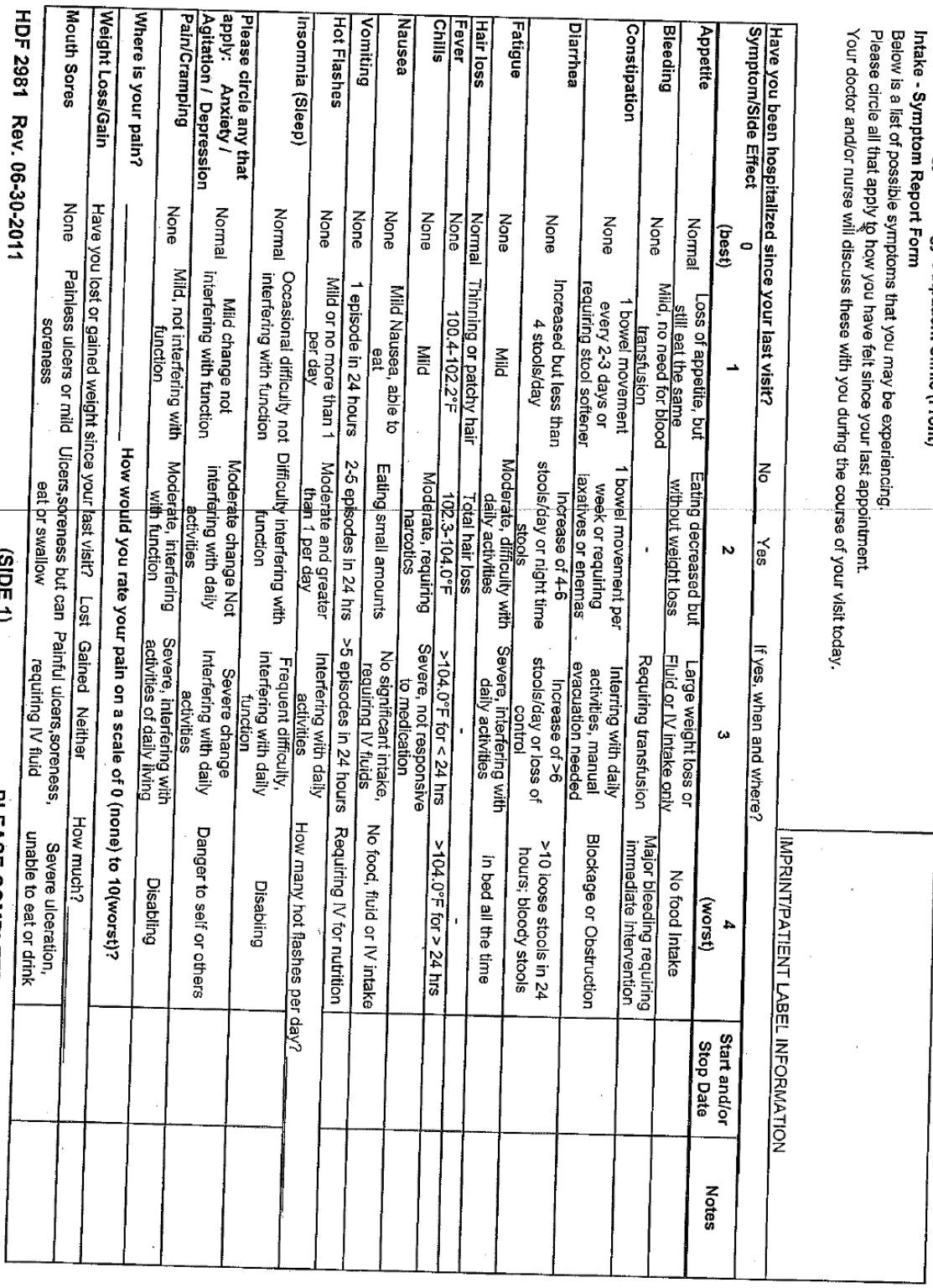
11.0 APPENDICES

11.1 Appendix A ECOG Performance Status[11]

Grade	Activity Level
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all self-care but unable to carry out any work activities. Up and about >50 percent of waking hours
3	Capable of only limited self-care; confined to bed or chair >50 percent of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair
5	Dead

11.2 Appendix B. UNCH Hematology Oncology Outpatient Clinic Intake – Symptom Report Form



UNCH Hematology Oncology Outpatient Clinic (Front)
Intake - Symptom Report Form
Below is a list of possible symptoms that you may be experiencing.
Please circle all that apply to how you have felt since your last appointment.
Your doctor and/or nurse will discuss these with you during the course of your visit today.

IMPRINT/PATIENT LABEL INFORMATION

Have you been hospitalized since your last visit?		No	Yes	If yes, when and where?			
Symptom/Side Effect	0 (best)	1	2	3	4 (worst)	Start and/or Stop Date	Notes
Appetite	Normal	Loss of appetite, but still eat the same	Eating decreased but without weight loss	Large weight loss or Fluid or IV intake only	No food intake		
Bleeding	None	Mild, no need for blood transfusion	-	Requiring transfusion	Major bleeding requiring immediate intervention		
Constipation	None	1 bowel movement every 2-3 days or requiring stool softener	1 bowel movement per week or requiring laxatives or enemas	Interring with daily activities, manual evacuation needed	Blockage or Obstruction		
Diarrhea	None	Increased but less than 4 stools/day	Increase of 4-6 stools/day or night time stools	Increase of >6 stools/day or loss of control	>10 loose stools in 24 hours; bloody stools		
Fatigue	None	Mild	Moderate, difficulty with daily activities	Severe, interfering with daily activities	In bed all the time		
Hair loss	Normal	Thinning or patchy hair	Total hair loss	-	-		
Fever	None	100.4-102.2°F	102.3-104.0°F	>104.0°F for < 24 hrs	>104.0°F for > 24 hrs		
Chills	None	Mild	Moderate, requiring narcotics	Severe, not responsive to medication			
Nausea	None	Mild Nausea, able to eat	Eating small amounts	No significant intake, requiring IV fluids	No food, fluid or IV intake		
Vomiting	None	1 episode in 24 hours	2-5 episodes in 24 hrs	>5 episodes in 24 hours	Requiring IV for nutrition		
Hot Flashes	None	Mild or no more than 1 per day	Moderate and greater than 1 per day	Interfering with daily activities	How many hot flashes per day? ____		
Insomnia (Sleep)	Normal	Occasional difficulty not interfering with function	Difficulty interfering with function	Frequent difficulty, interfering with daily function	Disabling		
Please circle any that apply: Anxiety / Agitation / Depression	Normal	Mild change not interfering with function	Moderate change Not interfering with daily activities	Severe change Interfering with daily activities	Danger to self or others		
Pain/Cramping	None	Mild, not interfering with function	Moderate, interfering with function	Severe, interfering with activities of daily living	Disabling		
Where is your pain?	_____ How would you rate your pain on a scale of 0 (none) to 10(worst)?						
Weight Loss/Gain	Have you lost or gained weight since your last visit?			Lost	Gained	Neither	How much? ____
Mouth Sores	None	Painless ulcers or mild soreness	Ulcers,soreness but can eat or swallow	Painful ulcers,soreness, requiring IV fluid	Severe ulceration, unable to eat or drink		

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UNCH Hematology Oncology Outpatient Clinic (Back)

Symptom/Side Effect	0 (best)	1	2	3	4 (worst)	Start and/or Stop Date	Notes
Cough	Absent	Mild, relieved by non-prescription medication	Requiring prescription cough medication	Severe cough, coughing spasms interfering with sleep or daily activities	-		
Shortness of Breath	None	On exertion, but can walk 1 flight of stairs	On exertion, cannot walk 1 flight of stairs	With normal level of activity	At rest or requiring ventilator support		
Rapid Heartbeat	None	Present	Present with lightheadedness or shortness of breath	-	-		
Itching	None	Mild or localized	Intense or widespread	Intense and interfering with daily activities	-		
Skin Rash	None	Minimal, no itching	<50% of body with moderate itching	>50% of body with severe itching	Skin blistering and loss of skin		
Numbness/Tingling (Circle any that apply)	None	Mild, not interfering with function	Moderate, interfering with function	Severe, interfering with activities of daily living	Disabling		
Swelling (Hand or Foot)	None	Mild, not requiring medication	Moderate, requiring medication	Severe, unresponsive to meds, limiting function	Severe generalized swelling		
Headache	None	Mild headache, slight fatigue	Moderate headache, great fatigue	Severe headaches, interfering with function	Seizures or paralysis coma		
Urinary Pain	None	Mild pain or difficulty urinating	Moderate pain or difficulty urinating	Extreme pain or cannot urinate	-		
Urinary Frequency/ Urgency	None	Increase in frequency or at night up to 2x normal	Increase > 2x normal but < hourly	Hourly or more with urgency or requiring catheter	-		
Urinary Leakage/Incontinence	None	With coughing or sneezing	Spontaneous, have some control	No control	No control (may have fistula)		
Proctitis (Rectal Bleeding)	None	Rectal discomfort	Interfering with daily activities	Stool incontinence or interferring with daily activities; intervention	Perforation, bleeding, or damage requiring surgery		
Libido	Normal	Decrease in interest	Severe loss of interest	-	-		
Erectile Impotence	Normal	Mild (impaired but satisfactory)	Moderate (impaired, erectile aids needed)	No erections	-		
Vaginal Dryness	Normal	Mild	requiring treatment	interferes with sexual function, painful			
Date of Last Menstruation (or date of cessation) _____							

Additional comments/ are you experiencing any other symptoms not listed above? Please specify:

Performance Status:	0	1	2	3	4
(Office use only)					

Change in medication since last visit: ____YES ____NO

Date & Time: _____ Physician Signature: _____

Date & Time: _____ Nurse Signature: _____

Rev. 06-30-2011 (SIDE 2) **PLEASE COMPLETE BOTH SIDES**