Attn: Please replace the RECIST criteria in the appendix with the newer version.

Study Drug(s):
Erlotinib (Tarceva® tablets) **Investigational** Supplied by: OSI Pharmaceuticals, Inc.
Pemetrexed (Alimta) **Investigational** Supplied by: Eli Lilly

Study Title: Phase I/II Clinical Trial Of Combined Re-irradiation With Pemetrexed And Erlotinib Followed by Maintenance Erlotinib For Recurrent And Second Primary Squamous Cell Carcinoma of the Head and Neck

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Participating Institutions :

Comprehensive Cancer Center of Wake Forest University

UNC Lineberger Comprehensive Cancer Center

PROTOCOL SYNOPSIS

Phase I/II clinical trial. Patients with recurrent HNSCC or second primary will receive re-irradiation and the radiosensitizing drugs Pemetrexed and Erlotinib beginning with the first day of RT. Erlotinib dose will be escalated during the Phase I portion of the study. Maintenance Erlotinib will be continued until disease progression, unacceptable toxicity or to a maximum of 2 years. No randomization

Primary Objective: Phase I: Find MTD for Erlotinib recommended for phase II.
Phase II: Determine Progression Free Survival at 1 year.

SCHEMA

RE-IRRADIATION - IMRT - 6 WEEKS

30 daily fractions that deliver 2.0 Gy to areas of gross disease (6000 cGy total) and 1.8 Gy to the areas felt to be at highest risk of occult involvement (5400 cGy).

+

Start : day 1 of re-irradiation

***Pemetrexed**: 500 mg/m2 over 10 min, every 3 weeks x 2 administrations

+

Start : day 1 of re-irradiation

Phase I - Dose Escalation	**Phase II**
Erlotinib: 100/125/150 mg daily, for 6 weeks or until mucositis and dermatitis reduce to grade I	**Erlotinib:** established dosedaily, for 6 weeks or until mucositis and dermatitis reduce to grade I

Follow by →

Maintenance Erlotinib for 2 years

Erlotinib dosed according to smoking status at the time of maintenance treatment:

**Not actively smoking: 150 mg daily

**Actively smoking: 300 mg daily

*Patients will receive premedication as follows: 1. folic acid 350-1000 µg/day starting 5-7 days before the first dose of pemetrexed and continued for 3 weeks after the last dose of pemetrexed; 2. vitamin B12 1000 mcg 1 dose i.m. 1 week before the first dose of pemetrexed; 3. dexamethasone 4 mg po bid, days -1, 0 and 1 of each pemetrexed treatment.

**Actively smoking is defined as smoking an average of at least 10 cigarettes daily and smoking for at least one year.
Not actively smoking is defined as either not smoking, smoking an average of less than 10 cigarettes daily, or smoking for less than 1 year prior to enrollment.

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1. INTRODUCTION

1.1 Disease Background

Locoregionally failure remains a serious problem in the treatment of Head and Neck Squamous Cell Carcinoma (SCCHN), especially in patients with advanced primary stage disease, despite the progress made with definitive or adjuvant chemo radiotherapy (CRT) over radiotherapy (RT) alone. For SCCHN patients with high risk features after surgery, cumulative estimated 5-year incidence of locoregional relapse after postoperative CRT is 29-31% (1). Furthermore, second primary tumors in the Head and Neck develop in up to 30% of patients over 10 years due to field cancerization (2).

When recurrence or second primary tumors occur in previously radiated fields, there are limited salvage options. When possible and indicated, surgery remains the standard of care. Long term salvage is possible in this well-selected group, with 5 y survival of 15-35%. However this is feasible for a small subset of patients. Many patients are medically unfit for surgery or have unresectable disease because of disease extent or involvement of critical structures.

Inoperable patients are usually offered chemotherapy, with a median survival of 8-10 mo, with the most commonly used agents being cisplatinum and 5-fluorouracil. Newer agents have failed to show survival advantage. The 1y survival is less than 35% and overall survival (OS) beyond 2 y is almost never realized (1,3).

Long term survival rates of 17% at 5 years have been reported with re-irradiation in selective patients (3). However, tumor cells persisting through radiation are likely radioresistant and adding radiosensitizing drugs offers a method to enhance cell killing. Previously published data have demonstrated that re-irradiation with concurrent chemotherapy is feasible, however severe toxicity is not infrequent.

Two multi-institutional cooperative group trials of re-irradiation combined with chemotherapy in inoperable patients have been completed. RTOG 96-10 examined a split course regimen of radiation with concurrent 5-fluorouracil and hydroxyurea: Median survival (MS) was 8.2 mo, 1 y OS was 41.7% and 2 y OS was 16.9 %. Severe complications of grad 4 or 5 occurred in 23% of patients (4). The succeeding trial RTOG 99-11 used the same radiation schedule, but daily cisplatinum and taxol during radiation, with G-CSF during the off weeks. Median survival time was 12.1 mo and median progression free survival was 7.8 mo. 1 yr progression free survival was 35% and OS was 50.2% and 2 y OS was 25.9%. Acute toxicity grade 4 or 5 occurred in 28%. There were 8 fatal toxicities, 5 during treatment and 3 post-treatment (5). Improvement in survival can be observed in these 2 consecutive RTOG studies and these results corroborate reports of single-institution trials (6,7).

Both these multi-institutional trials as well as almost all single institutional reports used split-course RT (1.5 Gy bid, for 5 of 14 days, followed by 7 days break to a total of 60 Gy). In an attempt to eliminate RT breaks another schedule was investigated at University of Utah, with 2cGy administered daily to a total of

50Gy, combined with 5-fluorouracil and hydroxyurea on weeks 1 and 4. MS was 10.2 mo and 2y survival was 15%. This study demonstrates that it is feasible to deliver a continuous course of re-irradiation with minimal treatment breaks (8).

Reported studies of re-irradiation with concurrent chemotherapy demonstrate substantial toxicity. Some have questioned whether re-irradiation toxicity outweighs the potential benefits because the median survival of re-irradiated patients marginally exceeds that of chemotherapy alone. However, the high rates of loco-regional control and the 2-3 y survival rates appear superior. For this reason use of re-irradiation should be limited to the setting of a clinical trial. Current studies for head and neck cancers are adding biologic modifiers to standard chemotherapy in an attempt to decrease the acute toxicity (1).

1.2 Background on Re-irradiation

Three dimensional radiation simulation of patients using CT or PETCT helps to localize tumor precisely. Intensity modulated radiation therapy (IMRT) is a way of delivering radiation to specific locations and avoiding normal tissue. For example, IMRT has been demonstrated to help in parotid sparing for patients treated de novo. For this population of patients who have received prior radiation, re-irradiation of the smallest volume of tumor and normal tissue is desirable. Patients will only be eligible for this trial who have gross disease that can be adequately contoured and treated while delivering doses to normal tissues within the specified constraints. In this trial patients will be treated with 30 daily fractions that deliver 2.0 Gy to areas of gross disease (6000 cGy total) and 1.8 Gy to the areas felt to be at highest risk of occult involvement (5400 cGy).

1.3 Tarceva® Background

Tarceva® (erlotinib) is a selective small molecule inhibitor of the intracellular tyrosine kinase domain of the epidermal growth factor receptor (EGFR). This drug is approved for the treatment of non-small cell lung cancer and pancreatic cancer). In phase I clinical trials, diarrhea and skin rash were the main toxicities. Erlotinib has been tested in a phase II study of recurrent metastatic SCCHN, for a reported 4% response rate and a median survival of 6 months. In another phase II study of advanced SCCHN, erlotinib was evaluated in 115 patients at a dose of 150 mg/d. Patients had no more than one prior therapy for advanced disease. Rash was reported in 79% of patients, and the partial response rate was 4.3%, with 38.3% achieving stable disease, suggesting activity and tolerability of erlotinib in this group of refractory patients (9).

Anti-EGFR therapies are good candidates for combination with other treatment modalities, including chemotherapy and radiotherapy, due to their tolerable safety profile and non-overlapping toxicities (10). Tumor xenograft studies confirm that systemic administration of Erlotinib results in profound tumor growth inhibition when combined with radiation. Erlotinib was shown to enhance radiation response at several levels, including cell cycle arrest, apoptosis

induction, accelerated cellular repopulation, and DNA damage repair. Preliminary microarray data suggest additional mechanisms underlying the complex interaction between EGFR signaling and radiation response. These data suggest that the Erlotinib/radiation combination represents a strategy worthy of further examination in clinical trials (11). Moreover, EGFR tyrosine kinase inhibitors decrease VEGF expression by both hypoxia-inducible factor (HIF)-1-independent and HIF-1-dependent mechanisms with anti-angiogenic effect expected to further add to tumor killing and radiosensitizing efficiency. Tumors with high level of VEGF expression and high vessel density are often relatively resistant to radiation therapy (12).

Smoking status is an important predictor for benefit from Tarceva®. It has recently been found that patients who smoke metabolize the drug rapidly and may not achieve adequate drug levels. A phase I clinical trial has been completed that found the MTD of Tarceva® for patients who continue to smoke is twice that of patients who do not smoke. Thus, it appears that sensitivity to Tarceva® is dependent on achieving an adequate dose of the drug. In the maintenance part of the current study will dose Tarceva® according to smoking status (13).

1.4 Alimta® Background

Alimta® (Pemetrexed) is a multi-targeted antifolate that inhibits several folate-dependent enzymes that play roles in purine and pyrimidine synthesis. The principal toxicities of pemetrexed are neutropenia, diarrhea, nausea/vomiting, mucositis, and skin rash. These toxicities are more frequent in vitamin-deficient (folate and vitamin B12) patients, and can be ameliorated by the co-administration of folate and vitamin B12. The use of prophylactic dexamethasone is also recommended to reduce the frequency of severe skin rash (14-16). Pemetrexed exhibits significant antitumor activity in a broad spectrum of human tumors, including mesothelioma, pancreatic, colorectal, lung, head and neck, breast and cervix cancers. (17,18). Antifolates have been established in cancer treatment for many years and are widely used in combination with radiotherapy. The ability of pemetrexed to sensitize cells to ionizing radiation has been reported in preclinical studies (19). Laboratory data suggest the potential clinical efficacy of combining pemetrexed with radiotherapy for SCC tumors sensitive to pemetrexed. (20). Efficacy and safety clinical data of RT and pemetrexed have been reported for other types of cancers, such as esophageal cancer (21).

1.5 Study Rationale

The main goal of our project is to define a novel combination of radiosensitizing drugs which should be able to improve upon the previously reported efficacy of combined re-irradiation and chemotherapy, while reducing acute and late toxicity. We propose to do this by:

1) Using continuous RT to increase efficacy.

2) Using IMRT to improve contouring of tumor and avoid previously irradiated normal tissues.
3) Using radiosensitizing chemotherapy drugs with reduced general toxicity, such as pemetrexed.
4) Adding a radiosensitizing biologic agent, erlotinib which is expected to increase efficacy but not toxicity.
5) Continue administration of erlotinib as single agent maintenance treatment after conclusion of re-irradiation to prevent or delay cancer progression. This is a very high risk population expected to benefit from maintenance strategy. Moreover, erlotinib maintenance treatment is not expected to significantly affect quality of life.

1.6 Other Goals of Our Projects:

1.6.1 Evaluate swallowing impairment and quality of life

Evaluate swallowing impairment and quality of life as important parameters in weighing the benefits of re-irradiation (such measurements were previously reported by just one institution, University of Chicago in re-irradiation studies (6).

In HNSCC, both the disease and its treatment have the potential to significantly impact key functions, such as eating, speaking, and socializing. Although chemoradiotherapy regimens minimize surgery and consequently disfigurement, they have other significant immediate, delayed and potentially long-term side effects that may profoundly influence quality of life (QOL).

Radiosensitizing chemotherapy given in combination with radiation increases the severity of severe mucositis, sticky saliva, pain, dry mouth, hoarseness, skin irritation and difficulties in swallowing and tasting, with many of these symptoms persisting years after treatment completion. For example, List and colleagues (22) observed that on an intensive chemoradiotherapy regimen administered to previously untreated HNSCC patients, up to three-quarters of patients reported moderate to severe problems with dry mouth, swallowing, tasting, sticky saliva and hoarse voice. While there was some improvement in most symptoms over 12 months, there was little change in dry mouth, and over a third of patients continued to report difficulties with sticky saliva and swallowing. In addition, patients' diets remained extremely restricted with a half to three-quarters on a soft food diet at 12 months.

Longer follow-up (2-4 years post-treatment) of these patients suggested some continued recovery in ability to eat a full range of foods and comfort in eating with others, although a third still had significant restrictions in diet and there was little change in other QOL or symptom domains after twelve months. There are to date, very few, if any data on the impact of adding novel chemotherapeutics, such as pemetrexed and novel biologic agents, such as erlotinib, to radiation or re-irradiation. While such agents might be expected to add little toxicity, it is important to document short and longer –term QOL and performance/function. These evaluations are particularly important in re-

irradiation studies, where toxicity might outweigh the possible marginal benefit in survival. This study will be one of the first to prospectively assess QOL and performance up to 2-3 years post-treatment. The following assessment tools will be used:

1 **ECOG Performance Status Rating Scale** describes global functioning in terms of mobility.

2 ***The Performance Status Scale for Head and Neck Cancer (PSS-HN)*** (see Appendix 10) The PSS-HN is a clinician rated instrument consisting of assessment of three functions (subscales)*:* Normalcy of Diet, Eating in Public, and Understandability of Speech. The interviewer rates the patient on each scale based on the patient's responses to targeted questions. Scores on each subscale range from 0-100, with higher scores indicating better performance. It has been demonstrated to be reliable and valid in head and neck cancer patients. The site research nurse will determine the score on each of the subscales by performing a clinical evaluation and unstructured interview format. The PSS-HN takes approximately 5 minutes to complete.

a) The Normalcy of Diet subscale assesses the degree to which a patient is able to eat a normal diet. Ten food categories are arranged from easy-to-eat at the low end to hard-to eat at the high end. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. Scores are computed by assessing the highest-ranking food the patient is able to eat.

b) The Eating in Public subscale was designed to assess comfort in socializing, specifically the degree to which the patient eats in the presence of others. There are five categories describing the patients' eating patterns. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. Scores are computed based upon patient's report of with whom he/she eats and in what type of setting.

c) The Understandability of Speech subscale is a five-item scale, which assesses how well the patient can be understood by others, regardless of voice quality or nature of speech. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. The scores are computed by assessing the degree to which the observer is able to understand the patient's speech. In addition, sites will document feeding tube status, dentition, and presence or absence of a tracheostomy on case report forms.

3 ***Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N)*** (see Appendix 9) The FACT-H&N is a multidimensional, self-report QOL instrument specifically designed and validated for use with head and neck cancer patients. The core scale (FACT-G) consists of 27 core items assessing patient well-being in four areas: Physical, Social/Family, Emotional, and Functional. Items are rated on a five-point scale: 0-"not at all", 1- "a little bit", 2-"somewhat", 3- "quite a bit" and 4-"very much". This core questionnaire is supplemented with a twelve-item head and neck

subscale targeting head and neck related symptoms and side effects. Overall QOL is the sum of the core items of the FACT-G. The head and neck subscale is not included in overall summary score but will be looked at separately.

Specifically, swallowing function affects quality of life and often decreases during and following CRT (23,24). Eisbruch et al (25) studied swallowing in 29 patients before CRT, early and late post-CRT. They reported decreased base of tongue to posterior pharyngeal wall approximation decreased UES opening and laryngeal closure which resulted in aspiration after the swallow in approximately 60% of the patients post-CRT.

Although swallowing function has a strong probability to diminish throughout CRT, swallowing function in patients in an organ-preservation protocol may endure better than patients in a surgical protocol. Fung et al (26) investigated swallowing ability in patients who all received chemotherapy originally but who received a subsequent laryngectomy for less than a 50% response compared to the patient group who did have greater than a 50% response who then underwent concurrent Chemoradiation followed by two cycles of adjuvant chemotherapy. Eighty-nine percent of the patient group who was able to continue the organ-preservation protocol was able to sustain nutrition on oral intake alone compared to only 64% of the laryngectomy group.

One of the challenges in evaluating swallowing function pre- and post CRT is the ability to quantify swallowing pathophysiology. Our institution is uniquely positioned to quantify swallowing physiology. We are one of the few facilities in the country that offer pharyngeal and upper esophageal sphincter manometry which measures pressures and timing of oropharyngeal swallowing ability. Furthermore, we will perform Flexible Endoscopic Evaluation of Swallowing (FEES) which provides information on swallowing function and appropriate diet level. Thus, we will obtain objective and instrumental pre-CRT data on swallowing function to objectively measure swallowing change as a function of time (i.e. 1-, 6-, and 12-months).

Swallowing treatment has recently been demonstrated to benefit patients undergoing CRT (27). Kulbersh et al (28) demonstrated improved swallowing quality of life in patients who began swallowing exercises prior to XRT and/or CRT. Accordingly, patients in the study protocol will be offered instruction in a swallowing home therapy program prior to beginning CRT. These exercises will be done by the patients twice a day, six days a week throughout the course of their CRT and for 6 months following CRT completion. Swallowing quality of life will be measured pre-CRT and at 1-, 6- and 12-months post CRT with a validated swallowing quality of life survey, M.D. Anderson Dysphagia Inventory (MDADI) (29).

1.6.2 Identify tumor biomarkers as possible predictors of treatment response and prognosis.

We have already established collaboration with our Mass Spectrometry/ Proteomics laboratory at Wake Forest University and we plan to evaluate the level of EGFR phosphorylation using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). Phosphorylation of specific tyrosine residues within the cytoplasmic domain of EGFR is part of the initial activation process that occurs upon ligand binding. These phosphotyrosine residues subsequently serve as docking sites for intracellular signaling molecules. During the past two decades researchers monitored EGFR phosphorylation in response to ligand binding and activation as a global immunologic measurement of total phosphorylation within intact EGFR. Measuring the accumulative changes in overall phosphorylation, rather than dynamic changes at specific sites might explain the failure in correlating the level of EGFR phosphorylation and activation with the response to EGFR inhibitors.

We plan to measure by nano LC-MS/MS the level of phosphorylation of different tyrosine residues within the cytoplasmic domain of EGFR in tumor tissue (primary tumor and nodal metastasis whenever tissue available) and compare with that in normal tissue from the same patient. Recruited adaptors to the EGFR phosporylated sites: Grb2, Shc, NSP1, and NSP2, SCK will be identified and measured in the same experiment. We will measure other molecules considered in the literature as markers of activation of different signaling pathways downstream of EGFR such as PLC-γ1, Cbl/Cbl-B, Ras-Raf-MEK-MAPKs, PI3K-Akt-ribosomal S6K, STAT 3, c-Src, SAPKs, PAK-JNKK-JNK and PKC and corroborate the results with the pattern of EGFR phosphorylation in the C-terminal region and with the recruited adaptors (30,31). We plan to corroborate these findings with P-AKT and P-ERK measured by classic immunohistochemistry (IHC) method and with the patients' response to treatment and prognosis.

We also plan to measure Thymidylate synthase (TS) and p53 levels in tumor tissue (as available) and correlate with response to treatment. Specific interaction exists between oncogenes and TS, by binding of TS protein to the p53 RNA, while wild type p53 can also inhibit TS promotor activity. In some preliminary clinical studies evidence was postulated for a combined predictive role for TS and p53 for response to antifolates such as Pemetrexed. TS and p53 will be measured by PCR or IHC, depending on tissue availability.

2. OBJECTIVES

2.1 Primary objective phase I

1) Evaluate acute toxicity and feasibility of the combined re-irradiation with radiosensitizing drugs: Pemetrexed and Erlotinib.

2) Determine MTD for Erlotinib, recommended for the phase II portion of the study.

2.2 Primary objective phase II

1) Determine Progression Free Survival at 1 year defined as the percentage of patients who are alive at 1 year after beginning of their concurrent re-irradiation and chemotherapy without loco-regional progression of their disease as measured by CT scan or MRI using RECIST 1.1 criteria (see Appendix 7) (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

2.3 Secondary objectives

1) Median Progression Free Survival, Median Overall Survival and Overall survival at 1 year and at 2 years.
2) Objective tumor response. .
3) Evaluate acute and chronic toxicity of the combined re-irradiation with radiosensitizing drugs: Pemetrexed and Erlotinib.
4) Measure QOL by standard survey forms: FACT-H&N, PSS-HN, and swallowing by direct functional measurements and by SWAL-QOL survey at different time points to evaluate the impact of treatment on QOL.
5) Biomarkers evaluation. Evaluate by nano LC-MS/MS in tumor tissue, reported to normal tissue, the level of phosphorylation of different tyrosine residues within the cytoplasmic domain of EGFR, bound adaptors, as well as markers of downstream pathways activation and corroborate with level of P-AKT and P-ERK evaluated by immunohistochemistry and with response to treatment. Measure level of TS and P53 and corroborate with treatment response.

3. TRIAL POPULATION

Phase I/II clinical trial. Patients with recurrent HNSCC or second primary will receive re-irradiation and the radiosensitizing drugs Pemetrexed and Erlotinib beginning with the first day of RT. Erlotinib dose will be escalated during the Phase I portion of the study. Maintenance Erlotinib will be continued until disease progression or to a maximum of 2 years. No randomization.

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

- Pathologically (histologically or cytologically) confirmed diagnosis of recurrent or second primary squamous cell carcinoma (SCC) of the oral cavity, oropharynx, hypopharynx, larynx, or recurrent neck metastases with unknown primary. Exception from pathology confirmation of tumor

recurrence is accepted for patients who originally had pathologically confirmed SCC of the Head and Neck, the new tumor is located in the head and neck area and it is clinically considered as a recurrence of the original tumor, and a tumor biopsy is technically difficult and would expose the patient to unjustified risk. The treating physicians should agree and document the clinical definition of tumor recurrence and should document the increased risk for biopsy.

- Patients will only be eligible for this trial if they have measurable tumor on the CTscan/MRI or by direct clinical/endoscopic evaluation.
- Subjects enrolled in phase II part of the protocol should not have metastastatic disease. However, patients with oligometastatic disease that can be treated with localized treatment with definitive intent are eligible.
- Patients should be found unresectable by a preliminary ENT evaluation or have refused surgery
- Prior history of head and neck radiation for Head and Neck Squamous Cell Carcinoma to no more than 72 Gy and most (>75%) of the recurrent or second primary tumor volume should be in areas previously irradiated to > 45 Gy.
- The entire tumor volume must be included in a treatment field that limits the total spinal cord dose to 54Gy (prior plus planned dose).
- Subjects must have recovered from the acute side effects of prior surgery, chemotherapy, or radiation therapy. A minimum time period at least 6 mo should have elapsed from prior radiation treatment until enrollment in the study.
- Patients may have received chemotherapy as a component of their primary tumor treatment but not for recurrent or metastatic disease. No prior treatment with systemic anti-EGFR inhibitors or Pemetrexed is permitted.
- ECOG performance status 0-1.
- Age ³ 18 years or older.
- ANC >1500/µl, platelet count > 100,000/µl. Total bilirubin < 1.5 and AST/ALT less than 2 times the upper limit of normal. Creatinine< 1.5 and creatinine clearance > 45.
- Subjects should be willing and able to take folic acid and vitamin B12 supplementation and should interrupt aspirin or other non-steroidal anti-inflammatory agents for a 5-day period (8-day period for long acting agents such as piroxicam) before entering the study.
- Informed consent must be obtained from all subjects prior to beginning therapy. Patients must provide verbal and written informed consent to participate in the study. Subjects should have the ability to understand and the willingness to give verbal and sign a written informed consent document

3.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria are not to be enrolled in this study:

- Patients with Nasopharyngeal Carcinoma.
- Subjects with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements, significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 3 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction.
- Patients with active Interstitial Lung Disease.
- Presence of third space fluid which cannot be controlled by drainage.
- May not be receiving any other investigational agents.
- Pregnant women are excluded from this. Breastfeeding should be discontinued. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control. Subjects who are women of childbearing potential and sexually active males must be willing to use effective contraception while on study.
- All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant
- HIV-positive subjects are excluded from the study.

3.3 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial.

3.4 Registration Procedure

All patients entered on any CCCWFU trial whether treatment, companion or cancer control trial must be registered with the CCCWFU Protocol Registrar. Patients should be registered prior to the initiation of treatment. The on study form (see Appendix 6) and prestudy flow sheet (see Appendix 13) should be completed prior to telephone registration and faxed to the registrar (336-713-6772). Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday. The form is appendix 6.

4. TREATMENT PLAN

4.1 Re-irradiation

All patients will receive re-irradiation. Radiotherapy will consist of 6 weeks of daily radiation using intensity modulated radiation

4.1.1 Dose Fractionation

RT will be given as one daily fraction for 5 consecutive days every week for six weeks. Total dose will be 60 Gy in 30 daily fractions to gross tumor.

Dose to the spinal cord must be limited to 54 Gy total (prior plus current). Decay factors are not permitted. Treatment will begin on Mondays, Tuesdays or Wednesdays. The exact time and date of each treatment is to be recorded. If the patient misses more than two days, i.e., two fractions, missed treatments (radiation with chemotherapy) should be made up.

A boost of an additional 6 Gy (to bring the total dose to 66 Gy) is allowed to a small area of gross residual disease assuming that dose to critical structures are not exceeded/

4.1.2 Physical Factors

Linear accelerators with appropriate photon and electron energies for supplemental boosting. Photon beams of ≥ 1.25 MeV and/or electron beams from 4-25 MeV are allowed. Treatment distance must be ≥ 80 cm SSD or greater, or ≥ 80 cm SAD for isocentric techniques.

4.1.3 Localization Requirements

Simulation of all fields is mandatory. Patients must be reproducibly immobilized. Radio-opaque markers should be used whenever possible to delineate the extent of nodal disease, skin involvement, and any gross disease. The use of customized blocks or multileaf collimation for field shaping is strongly recommended.

Treatment planning CT scans are required for IMRT treatment. Radioopaque contrast is recommended for better imaging. Beam localization films (portal films) should be obtained for all photon and electron fields.

4.1.4 Target Volume

The treatment fields should encompass the gross recurrent tumor with .5 cm margins needed to obtain the CTV. The treatment fields should encompass the recurrent tumor defined as the Gross Tumor Volume (GTV), considered all known disease defined by clinical radiographic or any other information available. Adequate margins should be added whenever possible. Margins less than .5 cm

are an acceptable deviation only in instances of spinal cord encroachment. A lower risk CTV may be included and will be taken to a lower dose.

A boost volume can be done after the CTV has received 60 Gy, c with additional 6 Gy in 3 fractions using electrons, photons, or IMRT planning. If a concomitant boost is desired with IMRT a CTV doses of 66 Gy will be indicated on the initial plan. The dose per fraction will be 2.2 Gy.

The Planning Target Volume (PTV) will provide a margin around each CTV (i.e. both the primary tumor and the lymph nodes containing clinical or radiographic evidence of metastases) to compensate for the variability's of treatment set up and internal organ motion. A minimum of 3 mm around the CTV is required in all directions to define each respective PTV. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

4.1.4.1 Planning

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including DVH analyses of the PTV and critical normal structures. A "forward" iterative planning or "inverse" planning using computerized optimization are allowed. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of noninvolved tissue as feasible.

Dose Specification

The prescription dose is the isodose which encompasses at least 95% of the planning target volume (PTV).

No more than 20% of any planning target volume (PTV) will receive >110% of its prescribed dose.

No more than 1% of any planning target volume (PTV) will receive <93% of its prescribed dose.

No more than 1% or 1 cc of the tissue outside the PTVs will receive >110% of the dose prescribed to the primary PTV.

Prescription dose to the PTVs shall be according to the following:

The gross tumor and lymph node will receive 30 fractions of 2.0 Gy/fraction, total 60 Gy.

The low risk CTV willreceive 30 fractions of 1.8 Gy/fraction, total 54 Gy.

4.1.5 Dose Calculation

Isodose calculations in the axial, sagittal, or coronal planes are required. In addition, dose volume histograms for the GTV and the spinal cord are required.

Independent of the treatment approach, the maximum dose to the spinal cord must be indicated on the daily treatment record. The specification of the protocol target dose is in terms of a dose to a point at or near the center of the

target volume. The inhomogeneity within the target volume should not exceed ± 10% of the target dose.

4.1.6 Evaluation Criteria

Dose and Fractionation
Total Dose Variation Fractionation Overall Evaluation
≤ 4 % ≤ 2 Days of non HFX Per Protocol
> 4% to ≤ 9% 3-5 Days of non HFX Variation Acceptable
> 9% > 5 Days of non HFX Deviation Unacceptable

4.1.7 Dose Modifications

Acute local toxicity (skin and mucosa) must be ≤ grade 3 at the beginning of each treatment week. If toxicity is > grade 3, treatment may be held up to two weeks until ≤ grade 3 is attained. Chemotherapy should be held until RT is resumed. Patients who cannot resume treatment within two weeks will be removed from study. These patients must be followed for survival.

If a treatment delay for local acute toxicity is required, only the dose of chemotherapy will be modified, not the total RT dose.

Treatment breaks must be clearly indicated in the treatment record. If treatment breaks unrelated to toxicity occur, e.g., department schedule, bad weather, or patient absence, the missed treatments should be made up.

There is a real, but relatively small risk of carotid rupture in patients whose tumors overlap the carotid artery. Most of these events have occurred in association with active tumor in this region and may not necessarily be due to adverse effects of treatment.

4.1.8 Treatment Verification

- For all forms of IMRT dose delivery, orthogonal films that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films.
- For all delivery techniques, except those that use a source of radiation that rotates during treatment, e.g. tomotherapy or IMAT, the intensity pattern for each gantry orientation shall be documented on a separate film. These films should NOT include the patient's anatomy.

4.1.9 Dosimetry Required

- For standard treatment approaches, an isodose distribution in a transverse plane through the center of the target volume is required summating all fields. If the spinal cord is in close proximity to the treatment volume, off axis isodose distributions should be performed as well.

- For 3D-CRT, isodose calculations in the axial, sagittal, or coronal planes are required. In addition, dose-volume histograms for the GTV and the spinal cord are required.
- For IMRT, isodose calculations in the axial, sagittal, or coronal planes are required. In addition, dose volume histograms for the GTV and the spinal cord are required. This documentation must indicate the planning system and version, e.g., Corvus, V. 3.1. Please provide a description of the treatment delivery system, e.g., IMRT compensating filter, MLC step and shoot, or dynamic tomotherapy.

4.2 Radiosensitizing drugs

4.2.1 Erlotinib (Tarceva®)

Erlotinib will be administered daily throughout radiotherapy, starting with day # 1 of RT. During Phase I portion of the clinical trial, erlotinib will be dose escalated starting with 100, 125 and 150 mg. If DLT is being encountered with the first dose level of Erlotinib, both drugs will be reduced by 25% and dose escalation restarted. The dose established as MTD or maximum dose of 150 mg will be used in the phase II portion of the clinical trial.

At the conclusion of RT the Erlotinib will be continued at the same dose until the dermatitis and mucositis reduce to grade I. The maintenance Erlotinb dose will then be started. Patients who had the erlotinib dose reduced because of erlotinib-related skin rash,during the CRT will continue the same dose of erlotinib as maintenance treatment. If this dose is lower than 75 mg daily, the patient will be discontinued from the study treatment. For all other patients the maintenance Erlotinib will be started at the dose of 150 mg/day for non-smokers or 300 mg/day for smokers (per smoking status defined at the time of the beginning of maintenance). The maintenance treatment will be continued until disease progression, unacceptable toxicity (see dose modification chart on section 7) or to a maximum duration of 2 years. Erlotinib dose should be adjusted per smoking status during maintenance treatment. Smokers are defined as patients smoking more than 10 cigarettes per day and for more than 1 year.

Tarceva® Tablets

Information on the clinical development and use of erlotinib (Tarceva® tablets) is contained in the Package Insert, Investigator's Brochure, and Guidance for Investigators**.** The package insert includes the NSCLC and pancreatic cancer indications. These documents should be reviewed prior to initiating the study.

4.2.1.1 Formulation

The pharmaceutical preparations of Tarceva® are formulations containing the hydrochloride salt. Tarceva® is supplied as tablets containing erlotinib

hydrochloride equivalent to 150 mg, 100 mg, and 25 mg of erlotinib. All tablets are round, white, film-coated, bi-convex tablets without markings. Additional information regarding Tarceva® can be found in the Package Insert.

4.2.1.2 Packaging and Labeling

Tarceva® tablets are supplied in blue-white, high-density polyethylene (HDPE) bottles of 30 tablets each.

4.2.1.3 Storage and Handling

Tarceva® tablets should be stored between 15°C and 30°C (59°F and 86°F).

4.2.1.4 Administration

Tarceva® tablets should be taken at approximately the same time of day. Each Tarceva® dose is to be taken with up to 200 mL (~ 1 cup or 8 oz) of water, and should be taken 1 hour before or 2 hours after meals or medications, including grapefruit juice, vitamins, and iron supplements. The entire dose must be taken at one time. If the patient vomits after taking the tablet(s), the dose is replaced only if the tablet(s) can actually be seen and counted.

Tarceva® will be supplied by OSI Pharmaceuticals

4.2.2 Pemetrexed (Alimta®)

All patients will receive Pemetrexed starting first day of radiation and continued every 21 days through the radiation. Pemetrexed dose will be 500 mg/m2 for all patients (unless reduced with 25% because of DLT encountered with the first dose level of Erlotinib) and will be given as a 10 min infusion.

Creatinine clearance will be calculated each time before administration of Alimta and the drug will not be administered if the creatinine clearance is < 45.

Patients will also receive Folic Acid (350-1000 µg) that must be given daily beginning approximately 5-7 days prior to first dose of Pemetrexed and continuing daily until 3 weeks after the last dose of study therapy. Patients will receive vit B12 1000 µg 1 dose i.m., 1-2 weeks before the first dose of Pemetrexed and will also receive Dexamethasone (4 mg of oral or equivalent) given twice daily on the day before, the day of, and the day after each dose of Pemetrexed, for rash prophylaxis unless medically contraindicated.

Because folic acid and vitamin B12 supplementation has significantly reduced the number of episodes of Grade 4 hematologic and Grade 3/4 nonhematologic toxicities associated with Pemetrexed therapy, a need for leucovorin as rescue agents is not anticipated. However, this section provides information should rescue be necessary. In clinical trials, leucovorin was permitted for CTC grade 4 leukopenia lasting > 3 days, CTC Grade 4 neutropenia lasting > 3 days, and immediately for CTC Grade 4

thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 muscositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100mg/m2 once, followed by 50 mg/m2 intravenously every 6 hours for 8 days.

4.2.2.1 Description and Handling Instructions

Pemetrexed: The freeze-dried drug product is composed of Pemetrexed and mannitol in a 1:1 ratio. Sodium hydroxide and/or hydrochloric acid solution may be added during processing to adjust the pH. Each 500mg vial contains Pemetrexed disodium equivalent to 510 mg of the base compound, Pemetrexed. The vial contains 2% excess to facilitate the withdrawal of the label amount the 500-mg vial. The drug product is stable when stored at room temperature.

4.2.2.2 Dosage

All patients will receive Pemetrexed starting first day of radiation and continued every 21 days through the radiation. Administration of more than two doses of Pemetrexed in the context of prolonged radiation treatment course due to interruptions will be at the discretion of the treating physician. Pemetrexed dose will be 500 mg/m2 for all patients, unless reduced with 25% because of DLT encountered with the first dose level of Erlotinib.

4.2.2.3 Administration

Reconstitute each 100 mg vial with 4.2 mL of 0.9% Sodium Chloride Injection (preservative free). Reconstitute each 500 mg vial with 20 ml of 0.9% Sodium Chloride Injection (preservative free). Reconstitution of either size vial gives a solution containing 25 mg/mL. Gently swirl each vial until power is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without affecting the product quality. Parenteral drug products should be inspected visually for particulate matter and discoloration. If particulate matter is observed do not administer. The reconstituted formulation is in the pH range of 6.8 to 7.5 and is not light sensitive.

Further dilution is required for administration. The appropriate quantity of the reconstituted solution must be further diluted in to a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume is 100 mL. Administer intravenously infusion over 10 minutes.

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride (preservative free). Physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore should not be used.

Chemically and physical stability of reconstituted and infusion solution were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature and lighting. When prepared as

directed, reconstitution and infusion solutions contain no anti-microbial preservatives. Discard any used portions.

Pemetrexed will be supplied by Eli Lilly.

4.2.3 Drug Accountability

Drug accountability will be maintained by the Drug monitor. These logs will record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication. A sample drug accountability form can be found in Appendix 3

Unused Tarceva® tablets should be destroyed on-site and OSI should be provided with documentation when this has occurred. Unused Alimta will be handled in accordance to Eli Lilly's drug accountability guidelines.

4.2.4 Concomitant Medications

All concomitant medications will be record as part of the patient's medical history and physical. All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented as concomitant medication.

4.2.4.1 Potential Drug-Drug Interactions

Erlotinib is both protein bound (92% to 95% in humans) and metabolized in the liver by CYP3A4 and, to a lesser extent, CYP1A2, and in the lungs by CYP1A1. A potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 and CYP1A2 inhibitors/inducers (see Appendix 15).

For patients who are being concomitantly treated with a potent CYP3A4 inhibitor, a dose reduction should be considered in the presence of severe adverse events (see dose reduction criteria for erlotinib-related toxicities, pg 33). For patients who are being concomitantly treated with a potent CYP3A4 inducer, alternative treatments that lack potent CYP3A4-inducing properties should be considered. Grapefruit juice is a CYP3A4 inhibitor that interferes with the metabolism of Tarceva. Therefore, consumption of grapefruit or grapefruit juice should be avoided during Tarceva treatment.

In addition, altered coagulation parameters and bleeding have been reported in patients receiving erlotinib alone and in combination with other chemotherapeutic agents and concomitant warfarin-derivative anticoagulants.

The mechanism for these alterations is still unknown. When warfarin is co-administered with erlotinib (anytime after Day 5), international normalized ratio (INR) and prothrombin time should be closely monitored and the anticoagulant dose should be adjusted as clinically indicated.

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure to erlotinib (AUC) by 46% and the maximum concentration (Cmax) by 61%. There was no change to Tmax or half-life. Therefore, drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Concomitant administration of Tarceva with 300 mg ranitidine, an H2- receptor antagonist, decreased erlotinib exposure [AUC] and Cmax by 33% and 54%, respectively. Therefore, co-administration of drugs reducing gastric acid production with Tarceva should be avoided where possible. Increasing the dose of Tarceva when coadministered with such agents is not likely to compensate for this loss of exposure.

Ibuprofen (400 mg qid) can be administered with Alimta in patients with normal renal function (creatinine clearance $\geq$ 80 mL/min), caution should be used when administering ibuprofen concurrently with Alimta to patients with mild to moderate renal insufficiency (CrCl from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of Alimta.

In the absence of data regarding potential interaction between Alimta and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following Alimta administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity

4.2.5 Supportive Therapy

Folic Acid, Vitamin B12, Dexamethasone, Leucovorin

Folic Acid (350-1000 µg) must be given daily beginning approximately 5-7 days prior to first dose of Alimta and continuing daily until 3 weeks after the last dose of study therapy.

Vitamin B_{12} (1000 µg) will be administered as an intramuscular injection approximately 1 week prior to first dose of Alimta and repeated approximately every 9 weeks until 3 weeks after the last dose of study therapy.

Dexamethasone (4 mg of oral or equivalent) given twice daily should be taken on the day before, the day of, and the day after each dose of pemetrexed, for rash prophylaxis unless medically contraindicated.

Because folic acid and vitamin B12 supplementation has significantly reduced the number of episodes of Grade 4 hematologic and Grade 3/4 nonhematologic toxicities associated with Alimta therapy, a need for leucovorin as rescue agents is not anticipated. However, this section provides information should rescue be necessary. In clinical trials, leucovorin was permitted for CTC grade 4 leukopenia lasting > 3 days, CTC Grade 4 neutropenia lasting > 3 days, and immediately for CTC Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis. The following intravenous doses and schedules of leucovorin were recommended for intravenous use: 100mg/m2 once, followed by 50 mg/m2 intravenously every 6 hours for 8 days.

Hematopoietic Growth Factors

The routine use of erythropoietic growth factors is strongly discouraged. Patients may receive erythropoietin or darbepoetin for anemia with Hb below 11g%. Granulocytic growth factors (e.g., filgrastim, pegfilgrastim) should be used only for neutropenic fever. Prophilactic antibiotic treatment with a quinolone of choice, at the discretion of the treating physician, should be administered for 14 days after second dose of pemetrexed if the patient reaches an ANC nadir of < 1000 / mm3 with the first dose of chemotherapy.

5.0 STUDY DESIGN

Phase I/II clinical trial. Patients with recurrent HNSCC or second primary will receive re-irradiation and the radiosensitizing drugs Pemetrexed and Erlotinib beginning with the first day of RT. Erlotinib dose will be escalated during the Phase I portion of the study. The treatment dose of erlotinib given concurrent with RT will be maintained until mucositis and dermatitis reduce to grade I. Maintenance dose of Erlotinib adjusted per smoking status will then be started and will be continued until disease progression, unacceptable toxicity (see dose modification chart on section 7) or to a maximum of 2 years. Patients who had the erlotinib dose reduced because of erlotinib-related skin rash,during the CRT will continue the same dose of erlotinib as maintenance treatment. If this dose is lower than 75 mg daily, the patient will be discontinued from the study treatment. No randomization.

Phase I dosing schedule of Erlotinib to reach MTD refer to safety endpoint in section 11.0 regarding DLT's.

Dose 1	100 mg
Dose 2	125 mg
Dose 3	150 mg

If 2 or 3 of the original 3 patients (or 3+ out of 6) of the first set of patients have a DLT at erlotinib (100 mg) then both pemetrexed and erlotinib both will be reduced by 25%.

	Pre-treatment 0-week1	Radiotherapy 6 weeks	Post RT Week 4	Post RT Week 8	Follow up
Erlotinib concomitant		Daily*			
Radiotherapy		daily			
Pemetrexed		500 mg/m2 q 21 days**			
Folic Acid	350-1000 µg, 5-7 days prior to 1st dose of pemetrexed	Daily and continue 3 weeks after last pemetrexed			
Vitamin B12	1000 µg i.m. single dose, 1 week prior to CRT.				
Dexamethsone		4 mg bid, days -1, 0 and 1 of pemetrexed treatment.			
Erlotinib maintenance			*Daily for up to 2 years		
Labs	X	X weekly	X	X	q 3 mo first 2 y, q 6mo 3rd year, yearly then.
ECG, ECHO/MUGA	X				
PET/CT	X			X	q 6 mo for 2 years then yearly (optional)***
CT/MRI tumor			X	X	q 6 mo for 2 years then yearly
Swallowing studies/ swallowing survey (MDADI)	X		X		at 5-7 mo and 11-13 mo
QOL surveys (FACT-H&N and PSS-HN)	X		X		at 5-7 mo 11-13 mo and 23-25 mo
Nutrition	X	X - weeks 2,4,6	X		at 6 mo and then as needed

* Erlotinb dose given concurrent with RT will be continued after the end of RT until dermatitis and mucositis reduce to grade I; Maintenance dose of erlotinb will then be started.
Patients will receive all necessary supportive care. In particular, we will offer preventive PEG placement before the beginning of treatment or later during the treatment for weight loss of more than 10% of initial body weight.
**Administration of more than two doses of Pemetrexed in the context of prolonged radiation treatment course due to interruptions will be at the discretion of the treating physician.
***PET/CT should be done in the same time with the CT neck with contrast whenever possible and approved by Medical Insurance.

Additional pre-treatment evaluations

1) Dental evaluation and treatment.
2) Nutritional evaluation for a prophylactic gastrostomy (PEG) tube placement anytime prior to treatment.
3) Swallow evaluation and instruction in swallowing home therapy.
4) Quality of life assessment and surveys.

6. CLINICAL AND LABORATORY EVALUATIONS

6.1 Pre-Treatment mandatory evaluations

Investigations			Timing
History, Physical Examination and Other Evaluations	• Medical history • PE • Height • Weight • BSA	• ECOG PS • Clinical tumor measurements • Prior therapy	Within 7 days prior to registration
Vital Signs	• Pulse[1] • BP[1]	• Temperature[1]	Within 7 days prior to registration
Hematology	• Full blood count with hemoglobin, platelets and differential[1]		
Biochemistry	• Na and K • BUN • Creatinine • Total bilirubin • Alkaline Phosphatase • Creatinine Clearance	• AST • ALT • Total protein • Albumin • Magnesium • Pregnancy Test[4]	
Radiology[2]	• CT scan or MRI		Within 14 days prior to registration
	• PET/CT scan		Within 28 days prior to registration
Other Investigations	• ECHO/MUGA[3] •		Within 6 months prior to registration
	• ECG[3]		Within 14 days prior to registration
Nutrition	• Consult and evaluation for PEG tube placement		Prior to beginning of CRT
Dentist	• Evaluation and treatment		Prior to beginning CRT
Quality of life evaluations	• Surveys: FACT-H&N (see Appendix 9), PSS-HN (see Appendix 10), MDADI (see Appendix 11)		Prior to beginning CRT
Speech pathology	• Evaluation of speech and swallowing		Prior to beginning CRT
Signs, Symptoms and Toxicities[5]	Baseline evaluation should document residual toxicity from previous therapy and any current signs and symptoms		Within 24 hours prior to CRT
Tissue/specimen submission[6]	Tumor and normal tissue biopsy, buccal mucosa scraping and blood collection (see Appendix 1)		Within 28 days prior to CRT
Smoker status	Complete the sample case report (see Appendix 2))		Within 7 days prior to CRT

1. To be repeated 72 hours prior to the start of CRT.
2. To ensure comparability, the baseline radiographs/scans and subsequent radiographs/scans to assess response should be performed preferably using identical techniques (eg, scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and preferably the same scanner). The same method, radiological or physical, should be employed and assessed by the same individual on each occasion if possible.
3. only if clinically indicated.
4. For women of childbearing potential only.
5. Signs, symptoms and toxicities will be graded according to the NCI CTCAE, v3.0. See Appendix 8
6. If patient consented to participate to tumor/blood component of the study

6.2 Mandatory evaluations during treatment and post-treatment

	Pre-Study entry	Weekly during treat.	From end of CRT				From start of treatment			
Assessments			Weeks				6 mos	9 mos	12 mos	Follow up
			2	4	6	8				
Evaluations										
Complete history/physical	X[a]	X[f]	X	X	X	X	X	X	X	X[k]
Medical Oncology Exam	X[a]	X[f]	X	X	X	X	X	X	X	X[k]
Pulse/ BP/ Weight/BSA/Temp/Height	X[a]	X[f]	X	X	X	X	X	X	X	X[k]
ECOG Performance Status	X[a]	X[f]	X	X	X	X	X	X	X	X[k]
Protocol –specific adverse events- see 7.4[b]	X[a]	X[f]	X	X	X	X	X	X	X	X[k]
Clinical tumor measurement	X[a]	X[f]	X	X	X	X	X	X	X	X[k]
Dentist	X[p]								X	
Imaging										
PET /CT scan	X[e]					X	Xo	Xo	Xo	X[o]
ECG	X[c,g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
ECHO/MUGA	X[u,g]									
CT Scan or MRI of tumor/primary site	X[c]			X		X	X	X[g]	X	X[k]
Laboratory Studies										
CBC, Differential, Platelets	X[a]	X	X	X	X	X	X	X	X	X[j]
Creatinine, BUN	X[a]	X	X	X	X	X	X	X	X	X[j]
Serum Electrolytes, MG, Ca^{++}, TB, AST/ALT,	X[a]	X	X	X	X	X	X	X	X	X[j]
Alk Phos, TP/Albumin	X[a]	X	X	X	X	X	X	X	X	X[j]
Creatinine clearence	X[a]	X[m]								
Pregnancy test	X[a,r]									
Quality of life assessments										
Swallowing studies/ swallowing survey (MDADI)	X[p]			X			X[q]		X[q]	
QOL and swallowing surveys (FACT-H&N, PSS-HN, MDADI)	X[p]			X			X[q]		X[q]	24 mo
Smoking status	X[s]			X		X	X	X	X	X
Nutrition evaluation	X[p]	X[f]	X[g]	X	X[g]	X	X		X	
Buccal muc. scraping / blood-correlatives	X[t,l]		X[e,l]	X[i,l]	X[i,l]	X[i,l]	X[i,l]	X[i,l]	X[i,l]	X[i,l]
Tissue (normal/tumor)	X[e,l]			X[i,l]	X[i,l]	X[i,l]	X[i,l]	X[i,l]	X[i,l]	X[i,l]

a	within 7 days prior to registration
b	toxicities will be graded according to the NCI CTCAE, v3.0.
c	within 14 days prior to registration
d	from patients who have consented to participate in the tissue/blood component of the study.
e	within 28 days prior to registration
f	weeks 2, 4, and 6 of CRT
g	if clinically indicated
h	last 2 weeks of treatment for FACT-H&N and PSS-HN only.
i	if tumor progression or recurrence
j	follow up will be performed every 3 mo in year two, every 6 mo in year three and yearly afterwards.
k	follow up CT scans or MRI will be performed every 6 mo in year 2 and yearly afterwards.
l	if patient has consented to participate in the tissue/blood component of the study.
m	before each administration of pemetrexed.
o	optional
p	prior to beginning CRT
q	performing the evaluation one month earlier or later is acceptable
r	for women of childbearing potential only
s	within 7 days prior to CRT
t	within 28 days prior to CRT
u	within 6 months prior to registration

Quality of Life Assessments

The Performance Status Scale for Head and Neck Cancer (PSS-HN) (see Appendix 10) consists of assessment of three functions (subscales): Normalcy of Diet, Eating in Public, and Understandability of Speech. The site research nurse will administer the PSSHN. Interviewers are encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. The interviewer rates the patient on each scale based on the patient's responses to targeted questions. The PSS-HN takes approximately 5 minutes to complete. It will be administered by the site research nurse initially before the beginning of treatment, then during the last 2 weeks of treatment and then at 1 mo, 5-7 mo, 23-25 mo.

Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N) (see Appendix 9) is a multidimensional, QOL instrument specifically designed for use with HNC patients that the patient can complete in 5-10 minutes. The site research nurse is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. It will be administered by the site research nurse initially before the beginning of treatment, then during the last 2 weeks of treatment and then at 1 mo, 5-7 mo, 11-13 mo and 23-25 mo.

The MD Anderson Dysphagia Inventory (MDADI) (see Appendix 11) is a survey specifically designed to assess dysphagia. It contains 20 questions directly addressing the swallowing function and several other general questions. It will be applied by the nurse in the Speech and Swallowing Section of the Department of ENT, initially once pre-treatment and then post-treatment, at 1 mo,

5-7 mo, 11-13 mo (when patients will also have direct functional assessment of swallowing by Dr. Susan Butler).

Interviewers are encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. It takes approximately 5-10 minutes to complete this survey.

7. DOSE MODIFICATION / TOXICITY MANAGEMENT

7.1 Radiation adverse events

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events (appendix 8).

Grade 3-4 therapy-induced mucositis and/or dysphagia, which are enhanced by radiosensitizing drugs, are expected to develop in majority of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube).

Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis.

Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations, and cervical myelopathy (<1% with restriction of spinal cord dose to ≤ 45 Gy).

7.2. Specific drug-related adverse event

7.2.1 Erlotinib

Adverse events associated with drug administration

The most frequently reported undesirable effects in cancer patients following administration of oral erlotinib as monotherapy are: dermatosis or rash (75%), diarrhea (54%), fatigue (52%), nausea (33%) and vomiting (23%).

Special Warnings and Special Precautions for Use

Interstitial Lung Disease (ILD): The overall incidence of ILD-like events in approximately 32,000 erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 1.1%. When cases from a postmarketing surveillance study from Japan are excluded, the incidence from rest of world was approximately 0.6%

Gastrointestinal Perforation: Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation.

Patients with Hepatic Impairment:
In a pharmacokinetic study (Study OSI-774-104) in patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 of 15 patients died on treatment or within 30 days of the last erlotinib dose. Six of the 10 patients who died had baseline total bilirubin > 3 x ULN suggesting severe hepatic impairment. None of the deaths were considered to be related to erlotinib treatment by the investigators. However, treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN. This study will not enroll patients with significantly abnormal liver function tests, per inclusion criteria.

Bullous and Exfoliative Skin Disorders: Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions.

Ophthalmologic Disorders: rare cases of corneal perforation or ulceration were reported. Erlotinib therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain. Infrequent occurrences of keratitis have been observed during erlotinib treatment. Isolated reports of uveitis and orbital cellulitis have been reported in patients receiving erlotinib therapy. Patients who develop irregular or excessive eyelash growth should be monitored for eye symptoms such as eye pain. Careful removal of in-growing/abnormal/elongated eyelashes should be considered if increased growth leads to scratching and/or irritation of the cornea. Patients with a prior history of ocular disorders or additional identifiable risk factors should be closely monitored by a physician. Patients with significant ophthalmologic abnormalities are excluded from this study.

If a patient experiences several toxicities, dose adjustments are to be made based on the greatest degree of toxicity (ie, reducing the dose to the lowest level). If significant toxicity is still apparent, the dose may be reduced a second time. Any patient who fails to tolerate treatment of 50 mg/day will be withdrawn from the study as indicated in the Table below.

Antidiarrheal and antirash medications may be introduced if clinically indicated. Previous Phase I and II studies have demonstrated the frequency and severity of diarrhea can be managed with loperamide. The recommended dose of loperamide listed in the Table below is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea resolves for 12 hours.

Skin rash or dermatosis has been observed during the first several days of treatment with Tarceva® in many patients and has been noted to diminish in severity despite continued treatment. No controlled clinical trials have been conducted to allow definitive recommendations on the treatment of Tarceva®-related rash. Patients who develop a rash characterized by pustules or raised red areas may be treated with oral minocycline (100 mg BID for 7 – 10 days to a maximum of 150 mg BID for 7 – 10 days as clinically indicated) at the discretion of the Investigator. Minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly. Moreover, Minocycline may decrease effectiveness of oral contraceptives with concurrent use. An additional form of birth control, such as barrier protection, is recommended.

Tarceva® dosing should be discontinued for any severe toxicity that does not respond to treatment or failure to recover within 14 days from hematological toxicity attributable to Tarceva®

DOSE REDUCTION CRITERIA FOR ERLOTINIB-RELATED TOXICITIES

Toxicity (NCI CTCAE v3.0)	Dose Modification [a]
Diarrhea	
Grade 1 or 2	None. Initiate therapy with loperamide[b]
Grade 3[c] or 4[c]	Interrupt Erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower[e].
Rash	
Grade 1	None
Grade 2	None. If rash persists and is interolable or worsens over 10 – 14 days, then reduce by 1 dose level and initiate treatment as outlined.[d,e]
Grade 3 [c]	Reduce by 1 dose lower[e]. If rash persists or worsens over 10- 14 days, then interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower[e].
Grade 4	Permanently discontinue Erlotinib
Interstitial Lung Disease	
Any Grade	If ILD is suspected, erlotinib should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, Erlotinib should be discontinued permanently and appropriate treatment instituted as necessary.
Other Toxicities	
Grade 1 or 2	None
Grade 3[c]	Interrupt Erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower[e].
Grade 4	Permanently discontinue Erlotinib

a) Doses that have been reduced for toxicity may be re-escalated one dose level only if the toxicity abates or returns to baseline severity and the investigator believes it is in the best interest of the patient. Doses that have been reduced from the highest dose level to the lowest may not be escalated back to the highest dose level. Any patient who fails to tolerate treatment at 50 mg/day will be discontinued from the study.

b) The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours.

c) If the event does not resolve to ≤ grade 2 within 14 days, Erlotinib will be discontinued

d) Dermatosis has been observed during the first several days of treatment with Erlotinib in many patients and has been noted to diminish in severity despite continued treatment. No controlled clinical trials have been conducted to allow definitive recommendations on the treatment of Erlotinib-related rash. Patients who develop a rash characterized by pustules or raised red areas may be treated with oral minocycline (100 mg BID for 7 – 10 days to a maximum of 150 mg BID for 7 – 10 days as clinically indicated) at the discretion of the Investigator. Minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly.

e) The erlotinib dose levels for the CRT portion of the treatment are the same as outlined in the dose escalation treatment planning (see 4.2.1) and depending on the initial dose, the next dose will be lowered with 25 mg. For the maintenance portion of the treatment the dose levels will be dependent on the smoking status of the patient at the time of maintenance treatment.: 1) for non- smokers the dose levels will be similar with the above (the CRT portion of the treatment) while for smokers the dose reduction will be in 50 mg decrements.

7.2.2 Pemetrexed

In NSCLC where Pemetrexed is FDA approved the most common reported adverse events are as follows:
The most common adverse events with pemetrexed for the treatment of patients with NSCLC are (33):

The most common adverse events (grades 3 and 4)	
Adverse event	%
anemia	8
leukopenia	5
neutropenia	5
fatigue	16
Thrombosis /embolism	3
Cardiac ischemia	3
anorexia	5
dyspnea	18
Chest pain	7
The most common clinically relevant adverse events (all grades)	
fatigue	87
anorexia	62
nausea	39
constipation	30
vomiting	25
diarrhea	21
Stomatitis / pharyngitis	20
dyspnea	72
Chest pain	38
Neuropathy /sensory	29
Infection without neutropenia	23
rash	17

For patients who develop or have baseline clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) before or during initiation of Alimta therapy, consideration should be given to draining the effusion prior to dosing. However, if, in the investigator's opinion, the effusion represents progression of disease, the patient should be discontinued from study therapy.

Therapy for Diarrhea

In the event of CTC Grade 3 or 4 diarrhea, the following supportive measures are allowed should be used: hydration, octreotide, and antidiarrheals. If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **must be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

Therapy for Patients with Diarrhea and Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

DOSE REDUCTION CRITERIA FOR PEMETREXED-RELATED TOXICITIES

Pemetrexed therapy should be discontinued if a patient experiences any hematologic or nonhematologic grade 3 or 4 toxicity after 2 dose reductions (except grade 3 transaminase elevations) or immediately if grade 3 or 4 neurotoxicity is observed.

Patients receiving pemetrexed therapy should be monitored for nadir and recovery before each dose and on days 8 and 15 after pemetrexed administration with a complete blood count, including a differential and platelet count. Periodic blood counts and chemistry tests should be performed to evaluate hematologic, renal, and hepatic function.

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts of maximum nonhematologic toxicity from the preceding cycle of therapy.

Toxicity (NCI CTCAE v3.0)	Dose Modification for Pemetrexed
Hematologic toxicity	
Nadir ANC< 500/mm3 and nadir platelets > 50.000/mm3	75% of previous dose
Nadir platelets < 50.000/mm3 regardless nadir ANC	50% of previous dose
Non-hematologic Toxicities Excluding Neurotoxicity	
Grade 1 and 2	100% of previous dose
Any grade 3 or 4 except mucositis and except grade 3 transaminase elevation	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of grade) or grade 3 or 4 diarrhea	75% of previous dose
Grade 4 mucositis lasting at least 3 days	75% of previous dose
Neurotoxicity CTC grade	
Grade 0-1	100% of previous dose
Grade 2	100% of previous dose

If on the day of scheduled treatment with Pemetrexed the absolute neutrophil count (ANC) is < 1200, or platelet count is < 75,000, hold treatment until ANC ≥ 1200 and platelets are > 75,000, then treat at a dose adjusted according to the ANC and /or platelet nadir.

7.3 Phase I portion of the study

For the Phase I portion of this protocol a standard 3+3 design will be used Erlotinib dose will be escalated from 100 mg to 125 mg and 150 mg po daily or until DLT develops in 2/6 patients. If 2 or 3 of the original 3 patients (or 3+ out of 6) of the first set of patients have a DLT at erlotinib (100 mg) then both pemetrexed and erlotinib will be reduced by 25%.

After the third patient at a given dose is accrued, enrollment will be suspended until 6 weeks after that patient completes therapy or until his mucositis or any other toxic effect at the end of treatment becomes less or equal to grade II, whichever comes first, to allow for monitoring of signs and symptoms of toxicity.

Dose-Limiting Toxicity (DLT) – For purpose of escalating/de-escalating the dose of erlotinib/ Pemetrexed, dose-limiting toxicity is defined as grade IV mucositis or dermatitis lasting more than 3 days, or grade III or IV mucositis lasting 6 weeks or longer from the completion of therapy, or any other grade III or IV toxicity, regardless of duration and which do not respond to treatment

(diarrhea, rash) or need to delay treatment for more than 2 weeks because of any type of toxicity during the re-irradiation segment of the treatment. Erlotinib and pemetrexed administration should be stopped if interstitial lung disease develops. Grade IV hematologic toxicity should not alter erlotinib dose or escalation. Pemetrexed dose should be adjusted accordingly.

7.4 Essential protocol-specific adverse events to be collected

Category	AE term	Ref. page in CTCAE
At baseline		
Gastro-intestinal	Dysphagia	21
Pulmonary/ Upper Respiratory	Edema, larynx (includes need or existence of tracheostomy)	57
During Treatment		
Pulmonary/ Upper Respiratory	Edema, larynx (includes need or existence of tracheostomy)	57
Gastro-intestinal	Dysphagia	
	Diarrhea	
Dermatology/Skin	Pruritus/Itching	21
	Rash/desquamation [face (out of RT field), trunk, extremities]	15
	Rash: Acne/acneiform	15
	Nail changes	15
	Rash inside the RT field: dermatitis associated with radiation- Select: Radiation (radiation dermatitis may be exacerbated by erlotinb and pemetrexed, but in-field skin changes are graded using the radiation scale)	15
	Rash inside the RT field: dermatitis associated with radiation- Select: Chemoradiation	15
During Follow up		
Auditory	Hearing	2
Pulmonary/Upper Respiratory	Edema, larynx (includes need for tracheostomy)	57
Gastrointestinal	Dysphagia (difficulty swallowing)	21
	Mucositis/stomatitis (clinical exam)- [specify oral cavity, pharynx, or larynx primary site]	24
Dermatology/Skin	Rash/desquamation [for late effects/scarring out of RT field – face, trunk, or extremities]	15
	Induration/fibrosis (skin and subcutaneous tissue)	44
	Osteonecrosis (includes necrosis of mandible, maxilla, skull)	45
Musculoskeletal/ Soft Tissue	Soft tissue necrosis (MUCOSAL ulceration requiring wound care, hyperbaric, or surgical intervention)	46
	Musculoskeletal/ Soft Tissue Soft tissue necrosis (DERMIS/SOFT TISSUE ulceration requiring wound care, hyperbaric, or surgical intervention)	46

8. CRITERIA FOR STUDY DISCONTINUATION

Patients should be discontinued from the study treatment in the following instances:

- Progression of disease
- Inability to tolerate erlotinib dose of 50 mg/day in CRT
- Inability to tolerate erlotinb dose of 75 mg /day for both non-smokers and smokers in the maintenance portion of their treatment
- Patients who require more than 2 weeks break from RT because of toxicity in the re-irradiation segment of the treatment
- Medical or ethical reasons, or noncompliance
- Patient request
- Patient death

The patients may be discontinued from the follow-up assessments for the following reasons:

- Patient refusal
- Patient's withdrawal of consent
- Patient death
- Patient noncompliance
- Patients who were unable to conclude the CRT portion of the protocol

9. REPORTING OF ADVERSE EVENTS

9.1 Adverse Event and Reporting Definitions

An adverse event or adverse experience is any untoward medical occurrence in a clinical investigation patient who is administered a medicinal product. An adverse event can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug are also considered as adverse events. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (eg, invasive procedures such as biopsies).

An AE does not include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the adverse event
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)

- Overdose of either study drug or concomitant medication without any signs or symptoms unless the patient is hospitalized for observation.

The relationship to study drug therapy should be assessed using the following definitions:

Not Related: Evidence exists that the AE has an etiology other than the study drug (eg. pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

Possibly/Probably Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the patient's clinical state, intercurrent illness or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon re-challenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

A serious adverse event is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- *Death*
- *Life-threatening situation (patient is at immediate risk of death)*
- *Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy, disease-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events)*
- *Persistent or significant disability/incapacity*
- *Congenital anomaly/birth defect in the offspring of a patient who received study drug*
- *Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.*

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
Development of drug dependency or drug abuse

For the Phase 1 portion of the study: All adverse events should be reported to the coordinating site within 24 hours of learning of the event.

A teleconference between all site Principal Investigator's will be held at least monthly to review toxicity data.

For the Phase 2 portion of the study: All serious adverse events should be reported to the coordinating site within 24 hours of learning of the event. For all other events, the adverse events log should be sent to the coordinating site within 5 business days of the patient being seen.

9.2 Reporting of Serious Adverse Events Associated with Erlotinib

All serious adverse events that are considered related to Erlotinb treatment must be recorded on a MedWatch 3500 Form (see Appendix 4) and faxed within one business day to:

OSI Drug Safety
Fax number: 303 546 7706

MedWatch 3500 Reporting Guidelines:

Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html and in Appendix 4.

In addition to completing appropriate patient demographic, suspect medication and reporter information, the report should include the following information within the Event Description of the MedWatch 3500 form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- *Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication*

For questions related to safety reporting, contact OSI Drug Safety at 303-546-7869.

Additional reporting requirements for grade 4 and grade 5 events: all grade 4 and grade 5 adverse events will be reported via the Safety and Toxicity Review Committee (STRC) notification procedure(see Appendix 5).

9.3 Reporting of Serious Adverse Events Associated with Pemetrexed

Study site personnel must notify Lilly or its designee in 24h of any "serious" (defined below) adverse event experienced by a patient.

Serious events are defined as those that result in:

- Death.

- Initial or prolonged inpatient hospitalization.
- A life-threatening situation (where the patient is at immediate risk of death).
- Severe or permanent disability.
- Congenital anomaly.
- Or, is significant for any other reason.

Serious adverse events will be collected for 30 days after the last dose of study drug and serious adverse events occurring 30 days after a patient is discontinued from the study will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure. Study-specific clinical outcomes of death because of disease progression are exempt from serious adverse event reporting, unless the investigator deems them related to use of the study drug. Hospitalization for study drug administration is not a serious adverse event.

In general, serious adverse events assessed as clearly being due to disease progression and not due to study drug(s) should be excluded from adverse event reporting. However, in cases where the specificity or severity of an event is not consistent with the risk information, the event should be reported.

Global Product Safety Fax Number for all SAEs for Pemetrexed is: 1-866-644-1697 or 317-453-3302.

10. EVALUATION OF RESPONSE

We will use RECIST (Response Evaluation Criteria In Solid Tumors) (see Appendix 7) for evaluation of response. For the purposes of this study, patients should be evaluated for response at 4 weeks after completion of RT, and then every 6 mo. In addition to a baseline CT scan/MRI scan, confirmatory scans should be obtained at 4 weeks, 8 weeks and every 6 mo afterward. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. PET/CT scans will be also performed at 8 weeks initially and then in the same time with CT scans (optional). PET/CT will not be used to define response, but mainly for early detection of relapse, second malignancies, distant metastasis.

10.1 Definitions

Measurable Disease and Non-measurable disease

Will be defined by Recist 1.1 criteria.

Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five

lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Non-target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes, mucosal lesions that can be delineated and measured by endoscopic examination). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

10.2 Response Criteria

- **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as

reference the smallest sum LD since the treatment started.

The non-target lesions will not be measured.

10.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.”

10.4 Confirmatory Measurement/Duration of Response

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

The **duration of overall response** is measured from the time measurement criteria are met for CR or PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The **duration of stable disease** is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression Free Survival at one year is defined as the percentage of patients who are alive at one year after beginning of their concurrent re-irradiation and chemotherapy without loco-regional progression of their disease as measured by CT scan or MRI using RECIST 1.1 criteria (see Appendix 7) (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Survival is measured from the first day of CRT to date of death.

10.5 Efficacy Endpoints

- Progression Free Survival and Overall Survival will be examined and reported at 1 year.
- Patients will continue to be followed up according to the above schedule and Median Progression Free Survival, Median Overall Survival as well as Overall survival at 1 year and at 2 years will be determined and reported.
- In addition tumor Objective Response measured by CT scan or MRI will be examined.
- In addition, quality of life as measured by speech, swallow, nutrition and pain will be examined.
- Biomarkers predictors of response and tissue prognostic markers will be searched as well.

  Using data from the RTOG 99-11 trial we will be able to compare with the 1-year PFS rate, as well as the 1-year and 2-year Overall Survival rates and Median Overall Survival measured and determined through our protocol.

10.6 Safety Endpoints

For the phase I portion of the study the definition of MTD for erlotinib is the primary endpoint. As secondary endpoints we will evaluate acute toxicity and tolerability of the combined re-irradiation with radiosensitizing drugs: pemetrexed and erlotinib.

Dose-Limiting Toxicity (DLT) – for purpose of escalating/de-escalating the dose of erlotinib/ Pemetrexed, dose-limiting toxicity is defined as grade IV mucositis or dermatitis lasting more than 3 days, or grade III or IV mucositis lasting 6 weeks or longer from the completion of therapy, or any other grade III or IV toxicity, regardless of duration and which do not respond to treatment (diarrhea, rash) or need to delay treatment for more than 2 weeks because of any type of toxicity during the re-irradiation segment of the treatment. Erlotinib and pemetrexed administration should be stopped if interstitial lung disease develops. Grade IV hematologic toxicity should not alter erlotinib dose or escalation. Pemetrexed dose should be adjusted accordingly.

11. SAMPLE SIZE AND STATISTICAL CONSIDERATIONS

For the Phase I portion of this protocol a standard 3+3 design will be used. Here 3 patients will be enrolled at the first dose of erlotinib (100 mg). If there are no DLTs then the dose of erlotinib will be escalated from 100 to 125 mg. If 1/3 patients have a DLT at 100 mg then an additional 3 patients will be enrolled. If 0/3 of these patients have a DLT then the dose of erlotinib will be escalated to 125 mg. If 1/3 of these additional patients have a DLT (total 2/6) at 100 mg then the MTD will be set at 100 mg. If 2 or 3 of the original 3 patients (or 3+ out of 6)

of the first set of patients have a DLT at erlotinib (100 mg) then both pemetrexed and erlotinib will be reduced by 25%.

After the third patient at a given dose is accrued, enrollment will be suspended until 6 weeks after that patient completes therapy or until his mucositis or any other toxic effect at the end of treatment becomes less or equal to grade II, whichever comes first, to allow for monitoring of signs and symptoms of toxicity.

If the first dose (100 mg erlotinib) is found to be tolerable (i.e., 0/3 patients have DLTs) then 3 additional patients will be enrolled at 125 mg. If 2/3 patients have a DLT at this level we will reduce the dose of erlotinib back to 100mg and test 3 additional patients at this dose. (Or if 3/6 have a DLT at this level we will reduce back to 100 mg (i.e., 1 /3 have DLT and then 2/3 additional patients have DLT).

If 125 mg erlotinib is found to be tolerable then 3 additional patients will be enrolled at 150 mg. If 2/3 patients have a DLT at this level we will reduce the dose of erlotinib back to 125 mg and test 3 additional patients at this dose. (Or if 3/6 have a DLT at this level we will reduce back to 125 mg (i.e., 1/3 have DLT and then 2/3 additional patients have DLT)

Thus, with this design a minimum of 9 patients are needed (3 at 100, 125 and 150 mg erlotinib) if no DLTs are observed and a maximum of 18 patients could be used if 6 patients were needed at all possible doses. Based on this dose escalation plan, the probabilities of dose escalation for various true DLT rates are given below:

True DLT Rate	Probability of Dose Escalation
20%	71%
30%	49%
40%	31%
50%	17%
60%	8%

For example, if the true DLT is 60% at a dose level, there is a 8% chance that the dose would be escalated. Once the MTD is determined an additional 22 patients will be enrolled into the Phase II portion of the protocol.

In the Phase II protocol there will be a total of at least 25 patients (possibly 28 patients if 6 are enrolled during the Phase I component at the chosen dose) evaluated at the chosen dose (3 (or 6) from the Phase I component and 22 additional patients). With this number patients enrolled we will be able to estimate the true 1 year PFS survival rate with a precision of no worse than +/- 19.6% when estimating a 95% confidence interval for the rate of PFS. The

following table shows the width of 95% confidence intervals for different 1-year PFS rates.

Proportion with 1 year PFS	Width of Confidence Interval with n=25
.30	+/- 18.0
.35	+/- 18.7
.40	+/- 19.2

In addition to estimating the 1-year PFS rate (with 95% confidence intervals), we will perform a secondary analysis that will compare this rate to that found in the RTOG 99-11 study (Sections 1.1 and 10.5).

Survival analysis method will also be used to estimate the median 1-year PFS and 1-year overall survival rates.

One-year, 2-year overall survival rates and median survival will also be compared between this protocol and the RTOG 99-11 study referenced in Sections 1.1 and 10.5.

In the Phase II component of the trial there will be additional secondary endpoints measured. These include quality of life assessments and swallowing assessments. For each of these measurements, we will assess the mean and 95% confidence intervals for continuous outcomes.

Many of these outcomes will be assessed at multiple time points, thus analyses examining repeated measurements will be made. In addition, a pre-post comparison will be made to assess the magnitude of change exhibited during the course of the protocol. This will be performed to assess the residual alterations of quality of life and swallowing.

We will be testing whether the post treatment outcomes measured at 12 months are improved (or worsened) from the pre-treatment levels. We will use paired t-tests to make these comparisons with the Null Hypothesis that there is no change in outcome versus a 2-sided alternative hypothesis that there is a change.

The goal of this test is to rule out a statistically significant worsening and still be able to detect an improvement if it occurs. A 95% confidence interval for the difference in the outcome measures will be constructed. If this interval includes 0, we will conclude that there is not conclusive statistical evidence that there is an improvement or worsening. If the interval does not include 0 we can determine whether there was a significant improvement (or worsening) depending on which side of the 0 the interval is on.

With 25 patients (at least) included in the Phase II component, we will have 80% power to detect an effect size of .584 with a 2-sided test using a paired

t-test to compare pre and post outcome (i.e. quality of life) levels. This implies that we can detect a difference equal to 58.4% of a standard deviation in the change in quality of life over time. Since there will be additional intermediate time points available for analysis, we can examine the change in quality of life taking these measurements into account and likely increase our precision when estimating the treatment effect.

In addition to the above efficacy related endpoints, we will examine acute and chronic toxicities that occur in this protocol. We will examine the grade and type of toxicities that occur and also compare these to what has been observed in previous trials (RTOG 99-11) to see whether the toxicity profiles of patients on this protocol are better than what has been observed previously. To do this we will compare mainly rates of Grade 4 and 5 toxicities between the two protocols using chi-square tests.

The total sample size for the Phase I plus II portions of this protocol will be between 31 and 40 patients. We expect to enroll about 9-10 patients per year. As soon as Phase I portion of the study is finished we might consider looking for another participating center, if needed, to try to finish the study enrollment in no more than 3 years.

12. TISSUE/SPECIMEN SUBMISSION

For patients who have consented to participate in the tissue/blood component of this study.

Wake Forest University encourages participants in protocol studies to consent to the banking of their tissue. Tissue Bank provides tissue specimens to investigators for planned and future translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, tissue and blood will be submitted to the Wake Forest University tissue bank for the purpose of conducting biomarker studies as described below and for banking for future translational research. Submission of tissue and blood is highly recommended.

Samples should be batch shipped when requested by Wake Forest. Samples can be shipped Monday through Thursday. The samples should be shipped overnight on dry ice to the following address:

Wake Forest Cancer Center
Tumor Tissue Core Facility
c/o Greg Kucera
Hanes Building Rm 4032

Medical Center Blvd
Winston-Salem, NC 27157

For accomplishing secondary objective 5 in section 2.3, every effort will be made to obtain tumor tissue as well as normal tissue for research purpose at the time of the initial biopsy performed for the diagnosis purpose, in order to avoid any additional biopsy procedure. The tumor samples collected from the patients will be stored in the Tumor Tissue Core Laboratory after appropriate preparations (see appendix 1). The same procedures will be applied in case of recurrent or progressive tumor. Whenever a patient has recurrent or progressive tumor that requires biopsy for diagnosis, we will ask for an additional piece to be removed and saved in the Tumor Tissue Bank for research purpose.

Buccal mucosa and blood samples will be collected before and after chemo-radiation treatment and at the time of tumor progression. Buccal mucosa samples will be saved in liquid nitrogen and blood samples will be stored as serum, plasma and buffy coat, after appropriate preparations (see appendix 1), according to the Tumor Tissue Core Laboratory protocol, approved and supervised by IRB. Although not required for participation in this study, collection of buccal mucosa and blood samples from patients before and after treatment with erlotinib is strongly encouraged. The saved buccal mucosa can be used in lieu of normal tissue if such a sample has not be banked.

The collection of patient tissue samples (neoplasms and matched adjacent normal tissue) is monitored by the Wake Forest University (WFU) IRB (Protocol Number BG98-391), including maintenance of patient confidentiality and the HIPAA-compliant sample database. The tissue as well as blood samples are kept in the Tumor Tissue Core Laboratory of the 4th floor of the Hanes Building, which is either manned by a member of the Tumor Tissue Core Laboratory or is locked at all times. The Core Lab's database resides on the Comprehensive Cancer Center of Wake Forest University's (CCCWFU) secure server behind the WFUHS firewall with HIPAA-compliant security. The database is only accessible by the Tumor Tissue Core personnel.

The Tumor Tissue Core Lab preserves tissues precisely characterized as to location and histology, and makes these samples available to investigators as fresh material for cell culture or as fresh-frozen tissues to be stored at -80^{o}C.

Our current standard procedures within CCCWFU are as follows:

1) the consent form includes language that allows for resected tissues to be used for research purposes as needed to meet the objectives of the current study and the blood and remaining tissue to be stored for future investigations;

2) samples are handled initially in the operating room pathology laboratory with a first priority that ensures that diagnostically relevant information is preserved prior to any research uses;

3) tissues for research use are only those that are deemed in excess of the materials normally necessary for diagnostic purposes and would otherwise be disposed as well as the biopsy specimens especially collected for research purpose.

4) the samples are collected and handled by personnel specifically trained to protect the integrity of the tissue and patient confidentiality;

5) tissues are preserved by fresh freezing in liquid nitrogen, unless a specific project requires a specialized use, such as the preparation of primary cultures, requiring different handling;

6) the samples are deidentified by giving samples from a given patient a unique code number that separates any patient information from the retrieved information about the sample in a secure database;

7) a Web-based search engine listing of specific information is derived from the Tumor Tissue Core database that is accessible only by investigators of the CCCWFU, and these search results contain information regarding the type of tissue and the numbers of samples available; and

8) the tissue is distributed to investigators of this trial for which it was collected to meet the proposed objectives. Blood specimens and additional remaining tissue can be accessed for future studies only after those future projects are reviewed by the WFU IRB and by the Tumor Tissue Committee, who oversee the research uses of tissues at the time of distribution.

Buccal mucosa and blood samples obtained at an outside institution will be processed in a similar manner (see appendix 1) and will be kept at -80^{o}C. Tumor specimens will be fresh-frozen in liquid nitrogen. Transportation to the Wake Forest University Tumor Tissue Bank will be assured by the Wake Forest University Tumor Tissue Bank on a regular basis.

According to the secondary objective 2.5 of this protocol we plan to evaluate the level of EGFR phosphorylation using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). Phosphorylation of specific tyrosine residues within the cytoplasmic domain of EGFR is part of the initial activation process that occurs upon ligand binding. These phosphotyrosine residues subsequently serve as docking sites for intracellular signaling molecules. We plan to measure by nano LC-MS/MS the level of phosphorylation of different tyrosine residues within the cytoplasmic domain of EGFR in tumor tissue (primary tumor and nodal metastasis whenever tissue available) and report it to that in normal tissue from the same patient. Recruited adaptors to the EGFR phosporylated sites: Grb2, Shc, NSP1, and NSP2, SCK will be identified and measured in the same experiment. We will measure other molecules considered in the literature as markers of activation of different signaling pathways downstream of EGFR such as PLC-γ1, Cbl/Cbl-B, Ras-Raf-MEK-MAPKs, PI3K-Akt-ribosomal S6K, STAT 3, c-Src, SAPKs, PAK-JNKK-JNK and PKC and corroborate the results with the pattern of EGFR phosphorylation in the C-terminal region and with the recruited adaptors. Measuring the accumulative changes in overall phosphorylation, rather than dynamic changes at specific sites

might explain the failure in correlating the level of EGFR phosphorylation and activation with the response to EGFR inhibitors.

We plan to corroborate these findings with P-AKT and P-ERK measured by classic immunohistochemistry method and with the patients' response to treatment and prognosis.

We also plan to measure Thymidylate synthase (TS) and p53 levels in tumor tissue (as available) and correlate with response to treatment. In some preliminary clinical studies evidence was postulated for a combined predictive role for TS and p53 for response to antifolates such as Pemetrexed. TS and p53 will be measured by PCR or immunohistochemistry, depending on tissue availability.

Any remaining tissue after performing the above mentioned research analysis as well as the blood specimens will be stored in our Tissue Bank and a separate IRB approved protocol will be required to access these specimens for future studies.

13. RETENTION OF RECORDS

Documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence should be retained for at least 2 years after the investigation is completed.

14. PUBLICATION PLAN

Plans to disseminate the results of this trial: We expect to be able to present the phase 1 results at the 2011 ASCO meeting. In addition we will submit these results to Journal of Clinical Oncology (JCO) in 2011.

The phase 2 trial results we expect to present to the 2012 ASCO meeting and we plan to submit the final phase 2 results to JCO in 2012. We expect to have a separate publication of quality of life and swallowing study results as well as a separate publication of correlative tissue results by 2013.

15. Multi-Institutional Monitoring Plan

15.1. SAE Reporting

Each investigator is responsible for submitting SAEs and unexepected AEs to their Institutional Review Board/Ethics Committee according to their institutional guidelines.

Any serious or unexpected event, which occurs to any patient in the course of their treatment on this study or within 30 days following cessation of treatment, must be reported immediately to WFU, by telephone 336-713-6767 within 24 hours of the investigator learning of its occurrence. When calling to report an event, please clearly state the protocol number (CCCWFU 60107) and the

patient identification number, along with the event description and grade. The immediate reports should be followed promptly by detailed, written reports.

Whenever FDA Form 3500 (MEDWATCH) must be faxed to OSI Drug Safety or to Eli Lilly for all SAEs which are unexpected, fatal or life-threatening experience and associated with the use of the drug, a copy must be faxed to WFU within 48 hours.

The patient must be followed up until clinical recovery is complete and/or laboratory results have returned to normal. This may mean that follow-up will continue after the patient has completed the trial.

15.2. Registration Procedures

All patients must be registered with the Protocol Office at Wake Forest University before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Research Nurse Coordinator Anne Flynn, RN, BSN at 336-713 6956 . To register a patient, call the Protocol Office at 336-713-6767 Monday through Friday, 9:00AM-4:30PM EST.

15.3. Study Monitoring

Personnel from the Protocol Office at the Wake Forest University will monitor the trial. Clinical Research Associates may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at each site will allow the monitor to review all source documents used in the preparation of the case reports. The Oncology Protocol Office at Wake Forest University can be reached at 336-713-6913 .

All study flow sheets should be sent to the CRA on a monthly basis for monitoring. Flow sheets may be sent via e-mail to Claire Kimbrough (ckimbro@wakehealth.edu) or faxed to 336-713-6773. Please make sure the cover page clearly identifies the source documents contained.

All study forms should be sent to the coordinating site within one week of patient completion.

15.4. Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Protocol Office at Wake Forest University Health Sciences.

- Written documentation of IRB approval of protocol (identified by title, protocol version and date of approval) for each site.
- IRB membership list
- Current curricula vitae and documentation of professional licensure of the Principal Investigator and co-Investigators listed on the 1572.

- U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator at the participating center. The names of any sub-investigators at the participating center must appear on this form. Investigators must also complete all regulatory documentation as required by local regulations. This includes any required human subjects training required by the site's local IRB.
- Human subject protections documentation (e.g. NIH, CITI) for all research personnel (e.g. study coordinators, data managers and other research personnel).
- IRB approved study informed consent and HIPAA consent form. HIPAA consent language can be included within the study informed consent. Please note that all informed consent forms should be reviewed and approved by the WFU protocol office prior to submission to the site's designated IRB.
- Laboratory certifications (CAP, CLIAs) and laboratory reference value ranges for each laboratory listed on the site's 1572.
- Executed clinical research contract
- Any approval memos from IRB for protocols, continuing reviews, and approved informed consents
- Signed WFUHS Conflict of Interest Form

15.5 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. Any deviation from the protocol must have prior approval by the WFU Principal Investigator and must be recorded and explained.

15.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at WFU. The written amendment will be sent to investigators and must be submitted to the IRB at the investigator's site for approval. 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.

15.7 Record Retention

Study documentation includes all Case Report Forms, 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.

15.8 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 onto the flowsheet. 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 case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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17.0 APPENDICES

APPENDIX 1	Blood and Buccal Mucosa Collection Instructions
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APPENDIX 17	Specimen Log
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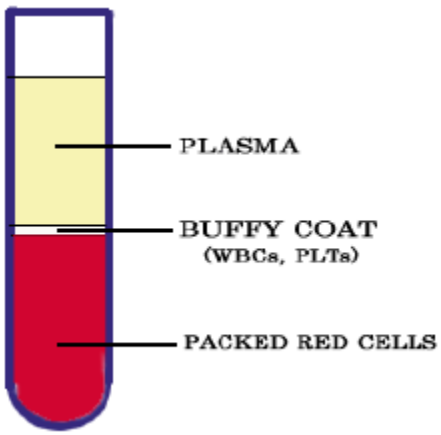
APPENDIX 1 Blood Collection Instruction

Serum Collection:
Using four (4) or more 1ml cryovials, label them with the study and case number, collection date and time, and clearly mark cryovials “serum”.
Process:
1. Allow one 5ml red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 min.
3. Aliquot a minimum of 0.5 ml serum into each of the four 1ml cryovials labeled with the study and case numbers, collection date and time, and clearly mark specimens as “serum”.
4. Store serum at –80° Celsius in Dr. Kucera’s lab until ready to use.
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma:
Using three (3) or more 1ml cryovials, label them with the study and case number, collection date and time, and clearly mark cryovials “plasma”.
Process:
1. Centrifuge specimen within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully pipette and aliquot a minimum of 0.5ml plasma into each of the 1ml cryovials labeled with the study and case numbers, collection date and time, and clearly mark specimens as “plasma”.
4. Store at a minimum –80° Celsius in Dr. Kucera’s lab until ready to use.
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Buffy coat:

For explanation of Buffy coat, please refer to the picture below.



Using three (3) or more 1ml cryovials, label them with the study and case number, collection date and time, and clearly mark cryovials “buffy coat”.
Process:
1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).
4. Remove the buffy coat cells carefully and place into the 1ml cryovials labeled “buffy coat” (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date and time of collection.
4. Store buffy coat samples frozen in Dr. Kucera’s lab until ready to use.
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Buccal Mucosa
Recommended brushes: Cytosoft Cytology Brushes, Medical Packaging Corporation, cat # CYB/100. They can be provided by WFUCCC.

1. Brushings of cheek mucosa on both sides should be obtained.

2. An initial very gentle cleaning brushing on a larger area should be performed. Discard the brush.

3. After cleaning, use a new brush and brush gently (to avoid any bleeding), about 10 times up and down along the cheek mucosa. Rotate the brush 180^0 and repeat the procedure on the other cheek mucosa. Cut (as needed to fit in) and discard the brush tip in a 15 ml conical tube containing 5 ml of NS.

4. Transport immediately to the lab.

5. Process as described below:

This procedure is performed under aseptic conditions in the laminar flow hood.

a. Label one 1ml cryovial with study and case number, collection data and time, and clearly mark cryovial “buccal cells”.
b. Swirl brush in the solution contained within the 15mL conical tube to remove as much cellular material as possible.
c. Discard brush and centrifuge 15ml conical tube at 1500rpm for 10 minutes to pellet the buccal cells.
d. Remove pellet and place into 1mL cryovial. Removing some supernatant will occur, and that will be removed with the next centrifugation.
e. Centrifuge again at 1500rpm for 10 min and remove all remaining supernatant.
f. Store at a minimum of -80°C until ready to use.

APPENDIX 2 Example of Smoker Status Case Report Form

XXXX ASSESSMENTS

CIGARETTE SMOKING HISTORY AT REGISTRATION

Date of evaluation: _____
DD MMM YYYY

1. Please indicate **one** of the following:

☐ Subject never smoked cigarettes.

☐ Subject has smoked < 100 cigarettes in a lifetime and stopped.
Indicate when stopped: ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

☐ Subject has smoked > 100 cigarettes in a lifetime and stopped.
Indicate when stopped: ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year
Average number of cigarettes smoked per day: _____ Number of years smoked: _____

☐ Subject is currently smoking cigarettes.
Average number of cigarettes smoked per day: _____ Number of years smoked: _____

OTHER TOBACCO/NICOTINE HISTORY AT REGISTRATION

1. Please indicate **one** of the following:
☐ Subject **never** used other tobacco or nicotine products. ***Do not*** *complete question 2.*
☐ Subject **currently or in the past** has used other tobacco or nicotine products. *Complete question 2.*

2. If a user of tobacco/nicotine products, indicate frequency used and/or how long ago product use stopped.

Cigars/Pipes ☐ Not Applicable
Frequency used: ☐ at least once daily ☐ at least once weekly ☐ at least once monthly
Product stopped: ☐ current ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

Oral Tobacco Products ☐ Not Applicable
Frequency used: ☐ at least once daily ☐ at least once weekly ☐ at least once monthly
Product stopped: ☐ current ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

Nicotine Replacement Therapy ☐ Not Applicable
Frequency used: ☐ at least once daily ☐ at least once weekly ☐ at least once monthly
Product stopped: ☐ current ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

Other, please specify: _____ ☐ Not Applicable
Frequency used: ☐ at least once daily ☐ at least once weekly ☐ at least once monthly
Product stopped: ☐ current ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

APPENDIX 3 Example of Investigational Product Accountability Log

INVESTIGATIONAL PRODUCT:
BRIEF STUDY DESCRIPTION:
STUDY NUMBER: CCCWFU 60107 INVESTIGATOR NAME:
SITE NUMBER: SITE NAME:
DISPENSING UNIT (ie, pack, vial, tablet etc.):
STRENGTH:
DISPENSING AREA:

Date	Patient's Initials	Patient's I.D. Number	Dose	Quantity Dispensed or received	Balance Forward / Balance	Investigational Product Identifier	Expiry Date	Recorder's Initials

APPENDIX 4 MedWatch Form 3500 LINK

MEDWATCH REPORT

It is important that if a MedWatch report is needed the report is forwarded to STRC for review along with your initial report. Steps on how to report may be found at the following website:

http://www.fda.gov/medwatch/how.htm

A copy of the MedWatch report can be found at the following website: http://www.fda.gov/medwatch/safety/3500a.pdf.

APPENDIX 5 Mandatory (STRC) Safety and Toxicity Review Committee (Previously CROC) (SAE) Serious Adverse Event Notification Procedure

Mandatory STRC SAE Reporting Requirements – Revised 1/23/2012

This document describes STRC reporting and use of the electronic submission form that is submitted **for unexpected grade 4 and any grade 5 (death during treatment) SAEs on CCCWFU Institutional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI summary IV reporting guidelines, **CCCWFU Institutional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at CCCWFU. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for CCCWFU Institutional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to them for review. All Clinical Research Management (CRM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone, followed by informing the entire committee via the required email notification.

THESE REPORTING REQUIREMENTS APPLY TO EVERYONE WORKING WITH CANCER CENTER INSTITUTIONAL PROTOCOLS.

What is considered an SAE under this mandatory procedure?
Any **unexpected grade 4** event not including routinely experienced events per protocol (e.g. myelosuppression) and **all grade 5 events** (death on treatment) should be reported. The patient is considered "on-treatment" as defined in the protocol, which can extend days/weeks/months past the last date of actual treatment.

Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2 and Phase 3 Trials

	ADVERSE EVENT					
	Grade 1, Grade 2, Grade 3		Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected
Unrelated	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Unlikely	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Possible	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Probable	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Definite	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in the text of the approved protocol.**

STRC notification responsibilities of the person handling the reporting/documenting of the SAE:

1. Make a phone call to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to http://ccc.wakehealth.edu/oris/strc.aspx.
   This will ensure that all persons that the event applies to will be notified; remember to file a copy of your confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)
3. Ensure that you document that the appropriate persons on the STRC has been contacted.
4. Follow up with/update the clinical member of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the electronic STRC form:

1. ORIS Patient ID (PID)
2. Name of STRC Clinician notified/Date/Time/Comments.
3. Grade of event.
4. Is this related to protocol treatment?
5. Is suspension of the protocol needed?
6. Is any change to consent or protocol needed?
7. Was the nature or severity of the event unexpected?
8. Date of the event.
9. Brief description of the event using approved CTC version terminology.
10. Date of last study dose before event.
11. Relevant tests/labs.
12. **Most importantly make sure that the Investigator assigns attribution to the reported event (grade) using the appropriate CTCAE version for the protocol.**

The Clinical Members of STRC to Notify by Phone or Page:

Bayard Powell, MD – Director-at-Large, CCCWFU; Chair, PRC; Section Head, Hematology/Oncology. 6-7970 / 6-2701 / Pager 806-9308

Antonius Miller, MD – Hematology Oncology 3-4392 / 6-7414 / Pager 806-7789

Glenn Lesser, MD – Hematology Oncology 6-9527 / 6-0256 / Pager 806-8397

Kathryn Greven, MD – Vice Chair – Radiation Oncology. 3-3600 / Pager 806-8314

Marissa Howard-McNatt, MD – General Surgery 6-0545 / 806-6438

Definition of Unavailable: As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting your STRC notification form. The important criteria is that have taken reasonable steps to notify and document that you have initiated some type of contact to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY:

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made further communication directly with the investigator may be warranted. STRC reserves the right to agree with the investigator's assessment if STRC does not agree with the investigator STRC reserves the right to suspend the trial pending further investigation.

AMENDMENTS TO PREVIOUS REPORTS

If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

APPENDIX 6 **CCCWFU # 60107**

REGISTRATION GUIDELINES

The following guidelines have been developed in order to ensure timely registration of your patient.

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar within 24 hours of Informed Consent. For affiliate sites, please register patients with the CCCWFU Protocol Registrar within 72 hours. Patients should be registered prior to the initiation of treatment.

In order to ensure prompt registration of your patient, please:

1. Complete the Eligibility Checklist (attached)
2. Complete the Protocol Registration Form (attached)
3. Alert the WFUHS registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or
   e-mail.

   Contact Information:

   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.
4. Please fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, please provide a printout of the results. Please ensure that the most recent lab values are sent.

CCCWFU # 60107 Eligibility Checklist **Page 1**

Yes	No	N/A	Inclusion Criteria (All responses must be **YES** in order to enter study)	Eligibility Confirmation (registrar)
☐	☐	☐	Does the patient have pathologically (histologically or cytologically) confirmed diagnosis of recurrent or second primary squamous cell carcinoma (SCC) of the oral cavity, oropharynx, hypopharynx, larynx, or recurrent neck metastases with unknown primary?	
☐	☐	☐	Does the patient have disease with tumor measurable on the CT scan/MRI?	
☐	☐	☐	Does the patient have no definitive evidence of distant metastasis? (Not applicable for patients enrolled in the Phase I, first two Erlotinib dose levels)	
☐	☐	☐	Is the patient found unresectable by a preliminary ENT evaluation or has refused surgery?	
☐	☐	☐	Does the patient have a prior history of head and neck radiation for Head and Neck Squamous Cell Carcinoma to no more than 72 Gy and most (>75%) of the recurrent or second primary tumor volume should be in areas previously irradiated to > 45 Gy?	
☐	☐	☐	Is the patient's entire tumor volume included in a treatment field that limits the total spinal cord dose to 54 Gy (prior plus planned dose)?	
☐	☐	☐	Has the patient recovered from the acute side effects of prior surgery, chemotherapy, or radiation therapy? (A minimum time period of at least 6 months should have elapsed from prior radiation treatment until enrollment in the study.) If applicable, date of prior radiation therapy: _____/_____/_____ to _____/_____/_____	
☐	☐	☐	Has the patient has received chemotherapy as a component of their primary tumor treatment, but not for recurrent or metastatic disease? No prior treatment with systemic anti-EGFR inhibitors or Pemetrexed is permitted.	
☐	☐	☐	Does the patient have an ECOG performance status of 0-1?	
☐	☐	☐	Is the patient 18 years or older?	
☐	☐	☐	ANC > 1500/µl ___ ___.___	
☐	☐	☐	Platelet Count > 100,000/µl ___ ___.___	
☐	☐	☐	Total Bilirubin < 1.5 ___ ___.___	
☐	☐	☐	AST/ALT < 2X the ULN ___ ___.___	
☐	☐	☐	Creatinine < 1.5 ___ ___.___	
☐	☐	☐	Creatinine Clearance > 45 ___ ___.___	
☐	☐	☐	Is the patient willing and able to take folic acid and vitamin B12 supplementation and interrupt aspirin or other non-steroidal anti-inflammatory agents for a 5-day period (8 day period for long acting agents such as piroxicam) before entering the study?	
☐	☐	☐	Is the patient able to understand and willing to give verbal and written informed consent prior to beginning therapy?	

CCCWFU # 60107 Eligibility Checklist **Page 2**

Yes	No	N/A	Exclusion Criteria (All responses must be **NO** in order to enter study)	**Eligibility Confirmation (registrar)**
☐	☐	☐	Does the patient have Nasopharyngeal Carcinoma?	
☐	☐	☐	Does the patient have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements, significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 3 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction?	
☐	☐	☐	Does the patient have active Interstitial Lung Disease?	
☐	☐	☐	Does the patient have a presence of third space fluid which cannot be controlled by drainage?	
☐	☐	☐	Is the patient receiving any other investigational agents?	
☐	☐	☐	Is the patient pregnant? Breastfeeding should be discontinued. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control. Subjects who are WOCBP and sexually active males must be willing to use effective contraception while on study. If applicable, pregnancy test: Positive or Negative	
☐	☐	☐	If a WOCBP, has the patient been instructed to contact the Investigator immediately if they suspect they might be pregnant?	
☐	☐	☐	Is the patient known HIV-positive?	

Signature: _____ Date: _____

Please send source documentation with Eligibility Form.

CCCWFU # 60107 Protocol Registration Form **Page 3**

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-713-6772 or registra@wakehealth.edu.

CCCWFU # 60107 Eligibility Source Documentation Checklist **Page 4**
(to be submitted with Protocol Registration Form)

	Source Documents Needed	✓ or N/A
1	Pathology report confirming diagnosis of recurrent or second primary squamous cell carcinoma (SCC) of the oral cavity, oropharynx, hypopharynx, or recurrent neck metastases with unknown primary.	
2	CT scan/MRI showing patient has disease with measurable tumor.	
3	Source documentation showing no definitive evidence of distant metastasis.	
4	Dictation from preliminary ENT evaluation showing patient is unresectable or has refused surgery.	
5	Radiation treatment summary indicating that the patient has received prior head and neck radiation to no more than 72 Gy and most (> 75%) of the recurrent or second primary tumor volume should be in areas previously irradiated to > 45 Gy.	
6	Documentation that the entire tumor volume must be included in a treatment field that limits the total spinal cord dose to 54Gy (prior plus planned dose).	
7	Dictation documenting that patient has recovered from the acute side effects of prior surgery, chemotherapy or radiation therapy. If applicable, dictation documenting that a minimum time period of at least 6 months has elapsed from prior radiation treatment until enrollment in the study.	
8	Dictation documenting patient has not received chemotherapy as a component of their recurrent or metastatic disease and no prior treatment with systemic anti-EGFR inhibitors.	
9	Dictation documenting an ECOG performance status 0-1.	
10	Most recent MD dictation (H&P) documenting patient ≥ 18 years old.	
11	Lab report documenting all initial required lab values.	
12	Documentation that patient is willing and able to take folic acid and vitamin B12 supplementation and interrupt aspirin or other non-steroidal anti-inflammatory agents for a 5 day period (8 day period for long acting agents such as piroxicam) before entering the study.	
13	Copies of all informed consent documents.	
14	Dictation showing that the patient does not have Nasopharyngeal Carcinoma.	
15	Dictation showing that the patient does not have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements, significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 3 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction.	
16	Documentation that the patient does not have active Interstitial Lung Disease.	
17	Documentation that the patient does not have presence of a third space fluid which cannot be controlled by drainage.	
18	Documentation that the patient is not receiving any other investigational agents.	
19	Lab results indicating negative pregnancy test for WOCBP.	
20	Documentation that the patient is not known HIV-positive.	

APPENDIX 7 Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference: (http://ctep.cancer.gov/forms/quickrcst.doc)

1. ELIGIBILITY

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

2. MEASURABLE DISEASE

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.
Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and:

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

1.1.1 Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to

confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

1.2 Response Criteria

1.2.1 Evaluation of target lesions

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

1.2.2 Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	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 (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

1.2.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

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

1.2.4

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

1.2.5 Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

1.2.6 Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

1.2.7 Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

2 RESPONSE REVIEW

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

3 REPORTING OF RESULTS

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

APPENDIX 8 Common Toxicity Criteria Version 3

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events Version 3.0, DCTD, NCI, NIH, DHHS. March 31, 2003 (http://ctep.cancer.gov) Publish Date: May 22, 2003

APPENDIX 9 FACT-H&N

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP 1	I have a lack of energy	0	1	2	3	4
GP 2	I have nausea	0	1	2	3	4
GP 3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP 4	I have pain	0	1	2	3	4
GP 5	I am bothered by side effects of treatment	0	1	2	3	4
GP 6	I feel ill	0	1	2	3	4
GP 7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS 1	I feel close to my friends	0	1	2	3	4
GS 2	I get emotional support from my family	0	1	2	3	4
GS 3	I get support from my friends	0	1	2	3	4
GS 4	My family has accepted my illness	0	1	2	3	4
GS 5	I am satisfied with family communication about my Illness	0	1	2	3	4
GS 6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS 7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE 1	I feel sad	0	1	2	3	4
GE 2	I am satisfied with how I am coping with my illness ...	0	1	2	3	4
GE 3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE 4	I feel nervous	0	1	2	3	4
GE 5	I worry about dying	0	1	2	3	4
GE 6	I worry that my condition will get worse.....	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF 1	I am able to work (include work at home).....	0	1	2	3	4
GF 2	My work (include work at home) is fulfilling	0	1	2	3	4
GF 3	I am able to enjoy life	0	1	2	3	4
GF 4	I have accepted my illness.....	0	1	2	3	4
GF 5	I am sleeping well	0	1	2	3	4
GF 6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF 7	I am content wit the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
H&N 1	I am able to eat the foods that I like	0	1	2	3	4
H&N 2	My mouth is dry	0	1	2	3	4
H&N 3	I have trouble breathing.....	0	1	2	3	4
H&N 4	My voice has its usual quality and strength.....	0	1	2	3	4
H&N 5	I am able to eat as much food as I want	0	1	2	3	4
H&N 6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N 7	I can swallow naturally and easily	0	1	2	3	4
H&N 8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N 9	I drink alcohol (e.g. beer, wine, etc.).....	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods.....	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

APPENDIX 10 **Performance Status Scale for Head and Neck Cancer Patients (PSS-HN)**

PID _____ Date _____ Visit # _____

Common Functions evaluated:

1.) Eating in public _____
2.) Understandability of speech _____
3.) Normalcy of diet _____

The higher the score, the better the ability of the patient to function.

Choose one answer for each of the 3 parameters.

Parameter 1	Performance	Points
Eating in public	No restriction of place, food or companion (can eat out at any opportunity)	**100**
	No restriction of place, but restricts diet when in public (eats anywhere but limits diet to foods that can be handled easily like liquids)	**75**
	Eats only in the presence of selected persons in selected places	**50**
	Eats only at home in the presence of selected persons	**25**
	Always eats alone	**0**

Parameter 2	Performance	Points
Understandability Of speech	Always understandable	**100**
	Understandable most of the time; occasional repetition necessary	**75**
	Usually understandable; face-to-face contact necessary	**50**
	Difficult to understand	**25**
	Never understandable; may use written communication	**0**

Parameter 3	Performance	Points
Normalcy of diet	Full diet with no restrictions	**100**
	Peanuts	**90**
	All meats	**80**
	Carrots, celery	**70**
	Dry bread and crackers	**60**
	Soft, chewable foods	**50**
	Soft foods requiring no chewing	**40**
	Pureed foods	**30**
	Warm liquids	**20**
	Cold liquids	**10**
	Nonoral feedings (tube feeding, etc.)	**0**

APPENDIX 11 **The M.D. Anderson Dysphagia Inventory**

*This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing. The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you. Please read each statement and **CIRCLE** the response which best reflects your experience in the **past week**.*

My swallowing ability limits my day-to-day activities.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E2. I am embarrassed by my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F1. People have difficulty cooking or me.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E7. I do not feel self-conscious when I eat.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E4. I am upset by my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P6. Swallowing takes great effort.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E5. I do not go out because of my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F5. My swallowing difficulty has caused me to lose income.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P7. It takes me longer to eat because of my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P3. People ask me, “Why can’t you eat that?”

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E3. Other people are irritated by my eating problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P8. I cough when I try to drink liquids.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F3. My swallowing problems limit my social and personal life.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F2. I feel free to go out to eat with my friends, neighbors, and relatives.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P5. I limit my food because of my swallowing difficulty.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P1. I cannot maintain my weight because of my swallowing problems.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E6. I have low self-esteem because of my swallowing problems.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P4. I feel that I am swallowing a huge amount of food.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F4. I feel excluded because of my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

Thank you for completing this questionnaire!

APPENDIX 12 **ECOG *PERFORMANCE STATUS SCALE**

This scale and criteria are used to assess how a subject's disease is progressing, assess how the disease affects the daily living abilities of the subject, and determine appropriate treatment and prognosis.

ECOG PERFORMANCE STATUS *	
GRADE	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

*ECOG = Eastern Cooperative Oncology Group

APPENDIX 13 Master Flow Sheet

The Comprehensive Cancer Center of Wake Forest University

CCCWFU # 60107 **Clinical Flowsheet** **PAGE: _____**

Patient:			**PID #:**		
Unit Number:			**NCBH M.D.**		
Date: mm/dd/yy					
Cycle # / Day of Cycle	/	/	/	/	/
Temp / Pulse / Resp / BP	/ / /	/ / /	/ / /	/ / /	/ / /
Height/Weight/BSA in m2	/ /	/ /	/ /	/ /	/ /
ECOG PS					
WBC/ANC	/	/	/	/	/
Seg **/** Band / Meta / Lymph	/ / /	/ / /	/ / /	/ / /	/ / /
Mono / EOS / Bas / Pro	/ / /	/ / /	/ / /	/ / /	/ / /
Hgb / Hct / **Platelets**	/ /	/ /	/ /	/ /	/ /
Na / K / Cl / CO2	/ / /	/ / /	/ / /	/ / /	/ / /
BUN / **Creat** / Gluc / Ca, Mg	/ / /	/ / /	/ / /	/ / /	/ / /
Creatinine Clearence	/ /	/ /	/ /	/ /	/ /
Prot **/ Alb / T.Bili / AST**	/ / /	/ / /	/ / /	/ / /	/ / /
ALT / AP /	/ /	/ /	/ /	/ /	/ /
PregTest/ EKG	/ /	/ /	/ /	/ /	/ /
Others					
Tumor Evaluation					
Tumor size					
Nodes size					
Chest X-Ray					
CT Head and Neck					
CT scan Chest					
PET scan					
QOL Evaluations					
FACT-H&N					
PSS-HN					
MDADI					
Swallowing evaluation					
Chemotherapy Drugs:					
Tarceva (Erlotinib)					
Alimta (Pemexetred)					
Vit. B12					
Folic Acid					
Dexamethsone					
Leucovorin					
Others					
Toxicity:					
ECOG Performance Status					
Fatique					
Mucositis grade					
Nausea/vomiting					
Use of feeding tube					
Oral nutrition					
Skin					
Diarrhea					
Other:					
Physician's Signature					

PROG – Progression **NC** – No Change **ABN** – Abnormal **STAT**

ND – Not Done **So** – Study Ordered **WNL** – Within Normal Limits

APPENDIX 14 **CCCWFU Measurement Form**

Instructions: Complete and submit this form as required by the protocol. Do not leave any entries blank. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable or not done. Retain a copy for your records and submit original to the CCCWFU Data Management Center.

CCCWFU Study Number: _____ CCCWFU Patient ID: _____

Patient Name: _____ MRN: _____

WFUHS/Affiliate: _____

(Specify)

LIST ALL TARGET AND NON-TARGET SITES TO BE USED FOR RESPONSE

Date of Observation (mm/dd/yy)							
Cycle:							
TARGET LESIONS							
Response Status (CR, PR, SD, PD)							
List sites for response:	Means of Evaluation	Measurement	Measurement	Measurement	Measurement	Measurement	Measurement
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
Total sum of LD for all Target Lesions:							
NON-TARGET LESIONS							
Response Status (CR, Incomplete Response/SD, PD):							
List sites for response	Means of Evaluation	Measurement	Measurement	Measurement	Measurement	Measurement	Measurement
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
Observer Signature:							

APPENDIX 15 CYP3A4 and CYP1A2 Inhibitors/Inducers

CYP3A4 Inhibitors	CYP3A4 Inducers
delaviridine	efavirenz
indinavir	nevirapine
nelfinavir	barbiturates
ritonavir	carbamazepine
saquinavir	glucocorticoids
amiodarone	modafinil
aprepitant	phenobarbital
chloramphenicol	phenytoin
cimetidine	rifampin
ciprofloxacin	St. John's wort
clarithromycin	troglitazone
diethyl-dithiocarbamate	pioglitazone
diltiazem	rifabutin
erythromycin	
fluconazole	
fluvoxamine	
gestoden	
itraconazole	
ketoconazole	
mifepristone	
nefazodone	
norfloxacin	
norfluoxetine	
mibefradil	
verapamil	
grapefruit juice	

CYP1A2 Inhibitors	CYP1A2 Inducers
amiodarone	insulin
cimetidine	methyl cholanthrene
fluoroquinolones	modafinil
fluvoxamine	nafcillin
furafylline	beta-naphthoflavone
methoxsalen	omeprazole
mibefradil	tobacco

APPENDIX 16 **CCCWFU 60107 – PI: Dr. Porosnicu**
Swallowing Portion Data Collection Form

Participant Name: _____

Assessment Date: _____

Flexible Endoscopic Evaluation of Swallowing (FEES)		
Bolus Administered		**PAS Score (1-8)**
Thin Liquid		
Puree		
Solid		
DOSS Level (1-7): _____		
Diet Description:		

Appendix 17 Specimen Collection Log

Study short title	CCCWFU 60107 - Phase I/II Clinical Trial of Combined Re-Irradiation with Pemetrexed and Erlotinib Followed by Maintenance Erlotinib for Recurrent and Second Primary Squamous Cell Carcinoma of the Head and Neck

Record of retained specimen samples

Patient Initials	Patient Study Number	Patient consent provided? Y / N	Date sample collected (dd/mm/yy)	Sample Type	Storage location
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			
		☐Y ☐N			

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Appendix 18 CCCWFU 60107 Adverse Event Log **Page ____ of ____**

PI: ____________________ **PID: ____________________** **MRN: ____________________**

Adverse Event Description	**Cycle of Toxicity Onset**	**Start Date**	**Stop Date**	**AE Type**	**Grade (1-5) per CTC v. 3.0**	**Attribution**	**Dose Limiting Toxicity**	**Serious**	**Action Taken**	**Treating Physician Initials/ Date**
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: _______	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: _____ ☐N/A	
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: _______	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: _____ ☐N/A	
				☐Expected ☐Unexpected	☐Mild/1 ☐Moderate/2 ☐Severe/3 ☐Life-threatening/4 ☐Death/5	☐Related ☐Probably ☐Possible ☐Unlikely ☐Unrelated	☐Yes ☐No	☐No ☐Hospitalization ☐Disability ☐Birth Defect ☐Life-threatening ☐Death ☐Other: _______	☐None ☐Therapy Withheld ☐Therapy D/C ☐Therapy Adjusted ☐Other: _____ ☐N/A	