CLINICAL STUDY PROTOCOL

RANDOMIZED, PLACEBO-CONTROLLED, PHASE 2 STUDY OF INDUCTION CHEMOTHERAPY WITH CISPLATIN/CARBOPLATIN, AND DOCETAXEL WITH OR WITHOUT ERLOTINIB IN PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMAS AMENABLE FOR SURGICAL RESECTION

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PROTOCOL SYNOPSIS

Title of Study:	Personalized, randomized, placebo-controlled, phase 2 study of induction chemotherapy with cisplatin/carboplatin, and docetaxel with or without erlotinib in patients with head and neck squamous cell carcinomas amenable for surgical resection
Objectives:	The primary objective of this study is to assess: • major pathologic response among patients with locally advanced oral cavity squamous cell carcinomas treated with induction cisplatin/carboplatin, docetaxel and erlotinib prior to surgery, and to compare it with the major pathologic response among patients treated with cisplatin/carboplatin, docetaxel, and placebo, in the trial population overall and in biomarker-defined subgroups. The secondary objectives of this study are to assess: • Safety and toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 • Recurrence-free survival • Progression-free survival • Response rate and disease control rate, as determined by RECIST version 1.1 • Percentage of viable tumor cells in the surgical specimen • To correlate tissue and blood-based biomarkers with outcome and toxicity • Quality of life, determined by the self-reported FACT-HN questionnaire
Study Design:	This is a randomized, double-blind, placebo controlled, phase 2 study of docetaxel and cisplatin/carboplatin with or without erlotinib in patients with HNSCC of the oral cavity amenable for surgical resection. Patients will be randomized to: **Arm A —** induction chemotherapy with concurrent erlotinib; **Arm B —** induction chemotherapy with concurrent placebo The clinical trial is divided in two stages: stage I (biomarker discovery/testing of previous findings) and stage II (biomarker-guided therapy). Fresh tissue and blood will be collected prior to initiation of induction chemotherapy for biomarker evaluation. In stage I, patients will be equally randomized to the control and experimental arms irrespective of their biomarker status. Upon completion of stage I, the biospecimens collected will be analyzed in search of predictive markers of benefit from erlotinib. These analyses will be informed by correlative studies of other erlotinib-based trials in HNSCC conducted at M. D. Anderson, pre-clinical data and other emerging data in the literature as regards to benefit from chemotherapy and/or EGFR inhibitors in this setting. When appropriate, techniques and cut-offs will be standardized to determine the most

	practical, efficient, and robust biomarkers able to discriminate responders versus non-responders to chemotherapy+erlotinib. These biomarkers (herein referred to as erlotinib associated biomarkers [EAB]) will be CLIA certified (when appropriate) and incorporated into stage II. During stage II, patients will be adaptively randomized to the control or experimental arms according to their EAB status.
Number of Patients Planned:	100 patients
Target Population:	Patients with stage III, IVA or IVB resectable HNSCC of the oral cavity.
Duration of Treatment:	All patients will receive up to 3 cycles of chemotherapy with concurrent erlotinib (arm A) or placebo (arm B), followed by surgery. Post-operative (chemo)radiation will be delivered according to institutional guidelines and the best judgment of the treating physicians.
Diagnosis and Main Eligibility Criteria:	**Inclusion criteria**: 1. Suspected or histologically/citologically confirmed HNSCC of the oral cavity, stage III, IVA or IVB (according to the AJCC 7th edition). Patients with a suspected lesion may be enrolled and a baseline biopsy will be obtained as part of the study. If squamous cell histology is not confirmed, patients will be discontinued from the study. 2. Patients must have surgically resectable disease, in the opinion of the treating physician 3. Age $\geq$ 18 years. 4. ECOG PS $\leq$ 2 (Appendix C) 5. Adequate bone marrow, hepatic and renal function defined by: 6. ANC $\geq$ 1.5 x 10^9/L; 7. Platelet count $\geq$ 100 x 10^9/L; 8. ALT (SGPT) $\leq$ 1.5 x upper limit of normal (ULN); 9. Total bilirubin $\leq$ ULN (patient's with Gilbert's syndrome are eligible, even if total bilirubin is > ULN); 10. Alkaline phosphatase $\leq$ 2.5 x ULN; 11. Serum creatinine $\leq$ 1.5 x ULN. 12. Patients with reproductive potential (e.g., females menopausal for less than 1 year and not surgically sterilized) must practice effective contraceptive measures for the duration of study drug therapy and for at least 30 days after completion of study drug therapy. Female patients of childbearing potential must provide a negative pregnancy test (serum or urine) $\leq$ 14 days prior to treatment initiation. 13. Written informed consent to participate in the study according to the investigational review board (IRB). **Exclusion criteria**: 1. Histology other than squamous cell carcinoma. 2. Primary sites other than oral cavity.

3. Prior chemotherapy or biologic therapy for the same HNSCC. Prior chemotherapy or biologic therapy for a different previous HNSCC is allowed
4. History of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug (e.g., Crohn's disease, ulcerative colitis). Patients requiring feeding tubes are permitted
5. Other active solid malignancies within 2 years prior to randomization, except for basal cell or squamous cell skin cancer or in situ cervical or breast cancer or superficial melanoma.
6. Serious underlying medical condition which would impair the ability of the patient to receive protocol treatment, in the opinion of the treating physician.
7. History of allergic reactions to compounds of similar chemical composition to the study drugs (docetaxel, cisplatin, carboplatin, erlotinib or their excipients), or other drugs formulated with polysorbate 80.
8. Any concurrent anticancer therapy, excluding hormonal therapy for prostate or breast cancer.
9. Women who are pregnant or breast-feeding and women or men not practicing effective birth control.

Study Procedures/ Frequency:

Procedures:

The study will include standard procedures at baseline, during chemotherapy, at surgery, and at the end of treatment (approximately within 8 weeks after surgery).

At baseline, patients will be assessed for eligibility. A treatment history, medical history, smoking history, and current smoking status and tobacco use, and use of concomitant medications will be obtained. A physical exam will be performed, as well as a self-reported questionnaire for quality of life assessment (FACT-H&N), and an assessment of baseline symptoms and toxicities. Baseline blood-work for hematology, biochemistry, and blood-based biomarker studies will be obtained, as well as a pregnancy test (when appropriate), and baseline imaging studies. A new biopsy of the tumor will be obtained for histopathological examination and biomarker analysis.

Eligible patients will be stratified according to their nodal stage (N0/N1 versus N2/N3) and will be randomized to treatment arms A or B.

For both arms, prior to each chemotherapy cycle, a physical exam will be performed, and patients will be reassessed for symptoms and toxicity, Blood-work for hematology, biochemistry, pregnancy test (when appropriate) will also be obtained prior to each cycle. Imaging studies, as well as a self-reported questionnaire for quality of life assessment (FACT-H&N) and blood-based biomarker studies, and erlotinib PK will be obtained after the last dose of chemotherapy. Patients will receive up to 3 cycles of chemotherapy with concurrent daily erlotinib (arm A) or placebo (arm B).

Following chemotherapy (preferably within 3 to 6 weeks after the last chemotherapy cycle), patients will undergo surgical resection and tumor tissue will be obtained for histopathological and biomarker evaluation.

	An end of treatment evaluation is planned approximately within 8 weeks after surgery, and consists of a physical exam, symptoms and toxicities assessment (including retrospective evaluation of any unexpected surgical complications), blood-based biomarkers, and quality of life assessment. **Treatment Arms:** **Arm A = Chemotherapy with Concurrent Erlotinib** Docetaxel 75 mg/m^2 IV followed by cisplatin 75 mg/m^2 or carboplatin AUC 6 mg.min/ml IV on Day 1 of each 21 day cycle for a maximum of 3 cycles, plus erlotinib 150 mg PO daily continuously until the day before surgery (including the day before surgery). **Arm B = Chemotherapy with Concurrent Placebo** Docetaxel 75 mg/m^2 IV followed by cisplatin 75 mg/m^2 or carboplatin AUC 6 mg.min/ml IV on Day 1 of each 21 day cycle for a maximum of 3 cycles, plus placebo 150 mg PO daily continuously until the day before surgery (including the day before surgery). **Supportive Care:** Standard pre- and post-medications will be administered with docetaxel and cisplatin/carboplatin infusions. Growth factors (G-CSF support) are strongly recommended during chemotherapy.
Test Product, Dose, and Mode of Administration:	Erlotinib (arm A) or placebo (arm B) 150 mg PO daily.
Reference Therapy, Dose, and Mode of Administration:	Arms A and B: Docetaxel 75 mg/m^2 IV on day 1 every 21 days Cisplatin 75 mg/m^2 or carboplatin AUC 6 mg.min/ml IV on day 1 every 21 days
Criteria for Evaluation:	
Safety:	All patients who receive at least one study treatment will be included in the safety analysis. Frequency of AEs, SAEs, discontinuation of study drug due to AEs and changes from baseline laboratory parameter values will be evaluated.
Efficacy:	All randomized patients will be included in the efficacy analysis. Primary endpoint: Major pathologic response Secondary endpoints: recurrence-free survival, progression-free survival, response rates, percentage of viable tumor cells in the surgical specimen, quality of life, pharmacokinetics, and biomarkers.
Statistical Methods:	The clinical trial is divided in two stages: stage I (biomarker discovery/testing of previous findings) and stage II (biomarker-guided therapy), with 50 patients in each stage. The first 30 patients in stage I will be equally randomized between two arms, stratified by lymph node status (N0/1 vs. N2/3). Patients 31 to 50 will be adaptively randomized between the two arms based on major pathologic response and nodal status. In stage II, the next 50 patients will be adaptively randomized based on response, node status, and one predictive biomarker in order to maximize response probability based on patients' molecular profile. Adaptive randomization assigns patients into the control arm and the experimental arm with the randomization probability proportional to the

	treat success using the Bayesian adaptive method such that more patients will be treated with the better treatment (higher overall major pathologic response rate) compared with conventional equal randomization method. The design can also maintain the prespecified type I and type II error rates. The projected accrual rate is 3 patients per month. We expect that the study accrual will take approximately 3 years. We assume that we can identify one EAB as a predictive marker for the treatment group (cisplatin/carboplatin, and docetaxel with erlotinib) in Stage I. We also assume that the EAB positive rate is 50%. The major pathologic response rates under the null and alternative hypothesis in the overall population are 0.2 and 0.45. Detailed operating characteristics of the design based on simulation studies are described in the protocol. For the primary endpoint of major pathologic response, we will use the Bayesian probit model to assess the main effect of treatment, nodal status, and biomarker, and treatment by biomarker interaction. For other binary secondary endpoints, logistic regression model will be used to assess the effect of treatment and biomarker. Cox proportional hazards models will be used to assess the effect of treatment and biomarker on time to event outcomes (recurrence free survival and progression free survival).
Protocol Date:	11/11/2022

1 INTRODUCTION

There are over 500,000 worldwide and over 38,000 new cases in the US of cancer of the head and neck reported annually; most of these are epithelial in origin and therefore designated as squamous cell carcinomas (HNSCC). Two-thirds of patients present with locally or regionally advanced disease and therapeutic efforts have focused on local control with surgery, radiation therapy, chemotherapy, or combined-modality approaches. Worldwide, HNSCC represent the third most prevalent cancer, and within HNSCC, the most frequent site of origin is the oral cavity.

Most HNSCC overexpress the epidermal growth factor receptor (EGFR), and EGFR inhibitors have been evaluated in this setting, either as monotherapy[1] or combined with cytotoxic chemotherapy.[2]

Erlotinib (Tarceva®, OSI-774) is an orally active EGFR tyrosine kinase inhibitor developed for the treatment of non-small cell lung cancer (NSCLC), pancreatic cancer, and other solid tumors.

In most regions, erlotinib is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen. This indication is based on data from NCIC CTG Study BR.21, a randomized, placebo-controlled study of single-agent erlotinib at a dose of 150 mg daily. This trial demonstrated a statistically significant and clinically meaningful survival benefit, as well as delayed time to deterioration of lung cancer symptoms, in patients who received erlotinib.[3]

Erlotinib in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer. In some regions, the indication is restricted to patients with metastatic pancreatic cancer. This indication is based on data from NCIC CTG Study PA.3, a randomized, placebo-controlled study of erlotinib at a dose of 100 mg daily given in combination with gemcitabine IV versus gemcitabine alone. This trial demonstrated a statistically significant survival benefit in patients who received this combination.[4]

Although an overview of information pertaining to erlotinib is presented below, more comprehensive information is presented in the erlotinib Investigator's Brochure appended to this protocol.

1.1 Background Therapeutic Information

1.2 Clinical Experiences with Erlotinib

Rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache are the most frequently reported toxicities with exposure to single-agent erlotinib. Patients receiving erlotinib in combination with chemotherapy agents have generally experienced the same types of adverse events as with single-agent alone. Laboratory abnormalities are observed infrequently with erlotinib as a single agent. These abnormalities primarily involve changes in liver function tests, including elevation of ALT, AST, and/or bilirubin. These same abnormalities have occasionally been observed in patients receiving erlotinib and concomitant gemcitabine, as well as in patients receiving erlotinib concurrently with carboplatin and paclitaxel. Further information regarding nonclinical and clinical experience with erlotinib is provided in the erlotinib Investigator's Brochure.

1.2.1 Phase 1 Studies in Cancer Patients

In phase 1 studies in cancer patients, the maximum tolerated dose (MTD) of single-agent erlotinib has been determined to be 150 mg daily, with diarrhea being the dose-limiting toxicity (DLT) despite supportive antidiarrheal treatment. Several phase 1b studies have been conducted to evaluate the MTD and pharmacokinetics of erlotinib when combined with standard doses of common chemotherapy regimens. As expected, patients who received concomitant chemotherapy experienced more hematological toxicities including anemia, neutropenia, and thrombocytopenia than patients who received erlotinib as single-agent therapy.[5] No evidence of pharmacokinetic drug-drug interaction was noted with any of the chemotherapy regimens evaluated, with the exception of capecitabine and paclitaxel/carboplatin. Capecitabine appears to increase the exposure of erlotinib and erlotinib appears to increase the exposure of platinum, although the magnitude of these increases was considered to be not clinically relevant.

1.2.2 Phase 1b/2 Experience in Patients with Head and Neck Cancer

Erlotinib single agent was studied in a multicenter phase 2 trial involving 115 patients with recurrent / metastatic HNSCC. The overall objective response rate was 4.3%, whereas 38.3% of patients had stable disease (with a median duration of 16.1 weeks). The median progression-free survival was 9.6 weeks and the median overall survival was 6.0 months.[6]

Siu et al. evaluated the combination of cisplatin and erlotinib in a phase1 / 2 study of 51 patients with recurrent / metastatic HNSCC. The recommended phase 2 dose was determined as cisplatin 75 mg/m^2 every 21 days and erlotinib 100 mg/day. The intent-to-treat response rate was 21%, median progression-free survival was 3.3 months and median overall survival was 7.9 months. The combination was well tolerated, with minimal grade ≥ 3 toxicity.[7]

Kim et al. presented the results of an M. D. Anderson single-arm, phase 2 study of the combination of cisplatin, docetaxel and erlotinib in patients with recurrent / metastatic HNSCC. The first six patients in that trial received cisplatin 75 mg/m^2 every 21 days, docetaxel 60 mg/m^2 every 21 days and erlotinib 100 mg daily for the first cycle, escalated to cisplatin 75 mg/m^2 every 21 days, docetaxel 75 mg/m^2 every 21 days and erlotinib 150 mg daily for cycles 2-6, if well tolerated. After no clinically significant grade ≥ 2 toxicities were observed in the first six patients, all subsequent patients received cisplatin 75 mg/m^2 every 21 days, docetaxel 75 mg/m^2 every 21 days, and erlotinib 150 mg daily beginning at cycle 1. Routine prophylactic granulocyte colony-stimulating factor (G-CSF) support was required during all cycles (including cycle 1) after patient #18 had an episode of grade 4 neutropenic fever. Thirty-two out of 48 evaluable patients achieved an objective response to treatment (8% CR, 58% PR), and 25% of patients had stable disease. Median progression-free and overall survival were 6 and 11 months, respectively. The regimen was tolerable, and the most common treatment-related grade ≥ 3 toxicities were nausea (14%), diarrhea (14%), dehydration (14%), febrile neutropenia (10%), infection without neutropenia (8%) and skin rash (8%).[8]

William et al. recently presented the results of an M. D. Anderson phase Ib study of standard dose (150 mg/day) versus high dose (200 or 300 mg/day) erlotinib prior to surgery in patients with resectable HNSCC, with the primary endpoint of biomarker modulation. The median time on treatment was 19 days. Molecular analysis on pre- and post-treatment tumor and blood specimens are ongoing. In 21 patients with oral cavity cancers treated on that study, response rates by standard Response Evaluation Criteria in Solid Tumors (RECIST) were 33%, indicating that a substantial proportion of locally advanced oral cavity squamous cell carcinomas exhibit fast and dramatic tumor shrinkage to erlotinib, thus justifying further studies of EGFR tyrosine kinase inhibitors in this patient population, as well as correlative molecular markers that can predict response to treatment.[9]

1.3 Rationale for the Current Study

The EGFR monoclonal antibody cetuximab is the only biologic agent approved for treating HNSCC, based on improvements in overall survival when combined with radiation therapy for locally advanced disease[10] or when combined with platinum/5-FU for recurrent/metastatic disease (EXTREME trial)[2]. Erlotinib and other EGFR tyrosine kinase inhibitors have also demonstrated clinical activity in HNSCC, either as single agents[6,9,11,12] or in combination with chemotherapy[7,8,13]. EGFR inhibitors are now being investigated for the management of earlier-stage HNSCC, including incorporation to platinum-based induction chemotherapy,[14] and chemoprevention.[15]

Despite the relatively late stage of clinical development of EGFR inhibitors for HNSCC, no molecular biomarkers have been identified that predict response to EGFR-targeted therapies in this disease. The discovery and development of novel and robust molecular markers of sensitivity/resistance of HNSCC to EGFR inhibitors would have enormous significance in personalizing treatments for this patient population; this development could assist in (1) avoiding treatment exposure of patients unlikely to respond to these agents, thus reducing toxicity and cost; (2) reducing the likelihood that overall “negative” results in EGFR-inhibitor trials conducted in an unselected population would cause dismissing a drug that could be active in a subgroup of patients.

The addition of docetaxel to induction chemotherapy with cisplatin and 5-fluorouracil has been demonstrated to improve overall survival in patients with locally advanced HNSCC treated with radiation therapy or chemoradiation therapy as definitive treatment.[16,17] As a result, the use of induction chemotherapy prior to non-surgical therapy has become more common. However, the role of taxane-based induction chemotherapy prior to surgical resection in locally advanced HNSCC is yet to be determined.

Licitra et al. conducted a randomized study of surgery upfront versus induction cisplatin, 5-fluorouracil (3 cycles) followed by surgery in 198 patients with oral cavity squamous cell carcinomas. The study was terminated early due to slow accrual. There was no improvement in overall survival in the experimental arm, but induction chemotherapy led to significant downstaging and less need for destructive surgery (i.e., mandibulectomy) and/or post-operative radiation therapy. A pathologic response to PF was seen in 27% of patients with stage III and 18% of patients with stage IVA/B. Patients with a pathologic response to induction chemotherapy had a statistically significant improvement in
overall survival compared to patients with a suboptimal pathologic response.[18]

Moreover, the authors were able to identify a biomarker of response to induction chemotherapy: patients whose tumors lacked a non-functional p53 mutations had a statistically significant higher chance of achieving a pathologic response and prolonged survival, compared to patients whose tumors had a p53 mutation.[19] Zhong et al. evaluated the role of cisplatin, docetaxel, 5-fluorouracil for 2 cycles as induction chemotherapy followed by surgery, compared to surgery upfront in 256 patients with oral cavity squamous cell carcinomas. There was no improvement in overall survival, but induction chemotherapy reduced the risk of distant metastases, particularly in patients with clinical N2 disease. Patients with a pathologic response also had improved overall survival compared to patients with an unfavorable pathologic response to induction chemotherapy.[20] Taken together, these studies illustrate that: (1) induction chemotherapy can alter the natural course of oral cavity squamous cell carcinomas, as demonstrated by downstaging and a reduction in the risk of distant metastases; (2) pathologic response to induction chemotherapy can serve as a surrogate marker for long-term overall survival; (3) biomarkers, such as p53 mutations, may identify individuals more likely to benefit from induction chemotherapy. These findings led us to postulate that optimization of induction chemotherapy using novel agents and patient selection based on biomarkers could improve treatment outcomes of patients with oral cavity squamous cell carcinomas.

The present trial is the first personalized, randomized, placebo-controlled, phase 2 study of induction chemotherapy with cisplatin and docetaxel with or without erlotinib in patients with oral cavity HNSCC amenable for surgical resection. Our primary hypothesis is that the addition of erlotinib to induction chemotherapy will improve treatment efficacy (as assessed by pathologic response), particularly in a biomarker-defined subpopulation. If successful, this trial may assist in the development of a new standard-of- care, erlotinib-based, induction treatment in a biomarker-defined population of patients with HNSCC undergoing surgery.

Erlotinib was chosen as the experimental agent because of ease of administration, demonstrated activity when combined to cisplatin and docetaxel for treatment of metastatic HNSCC,[8] demonstrated activity as single agent when administered prior to surgical resection in patients with early/intermediate stage HNSCC (33% response rate in 21 patients with oral cavity cancers in our previous pre-operative single-agent erlotinib trial)[9], and availability of biospecimens from several HNSCC clinical trials conducted at M. D. Anderson using erlotinib-based therapies that can inform biomarker

evaluation for this study. These include the erlotinib prevention of oral cancer (EPOC) study (N=150 patients, completed), the erlotinib pre-operative study (N=40 patients, completed), the single-arm, phase 2 trial of cisplatin, docetaxel and erlotinib in metastatic HNSCC (N=50 patients, completed), and the randomized phase 2 trial of cisplatin, docetaxel with or without erlotinib in recurrent/metastatic HNSCC (N=120 patients, ongoing). Additionally, pre-clinical studies with erlotinib funded by the M. D. Anderson SPORE program (PI: Jeffrey Myers, MD, PhD) and the Conquer Cancer Foundation (William William, MD) are currently under way to determine the role of somatic mutations, protein expression profiles, non-coding RNAs and other molecular alterations in predicting activity of erlotinib in HNSCC. These experiments will also inform the development of predictive biomarkers for this clinical trial.

2 STUDY OBJECTIVES

The primary objective of this study is to assess:

- major pathologic response among patients with locally advanced oral cavity squamous cell carcinomas treated with induction cisplatin/carboplatin, docetaxel and erlotinib prior to surgery, and to compare it with the major pathologic response among patients treated with cisplatin/carboplatin, docetaxel, and placebo, in the trial population overall and in biomarker-defined subgroups.

The secondary objectives of this study are to assess:

- Safety and toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
- Recurrence-free survival
- Progression-free survival
- Response rate and disease control rate, as determined by RECIST version 1.1
- Percentage of viable tumor cells in the surgical specimen
- To correlate tissue and blood-based biomarkers with outcome and toxicity
- Quality of life, determined by the self-reported FACT-HN questionnaire

3 STUDY DESIGN AND PLAN

This is a randomized, double-blind, placebo controlled, phase 2 study of docetaxel and cisplatin/carboplatin with or without erlotinib in patients with HNSCC of the oral cavity amenable for surgical resection. Patients will be randomized to:

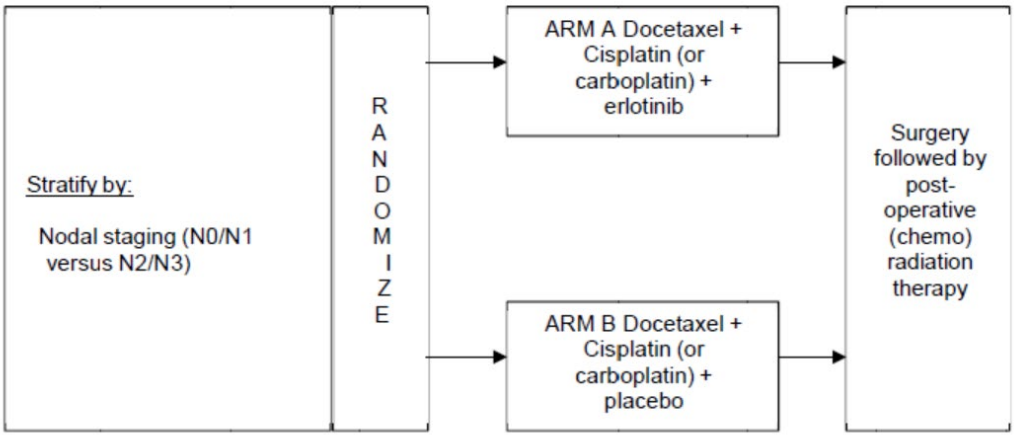
Arm A — induction chemotherapy with concurrent erlotinib;

Arm B — induction chemotherapy with concurrent placebo

The clinical trial is divided in two stages: stage I (biomarker discovery/testing of previous findings) and stage II (biomarker-guided therapy). Fresh tissue and blood will be collected prior to initiation of induction chemotherapy for biomarker evaluation. In stage I, patients will be randomized to the control and experimental arms irrespective of their biomarker status. Upon completion of stage I, the biospecimens collected will be analyzed in search of predictive markers of benefit from erlotinib. These analyses will be informed by correlative studies of other erlotinib-based trials in HNSCC conducted at M. D. Anderson, pre-clinical data and other emerging data in the literature as regards to benefit from chemotherapy and/or EGFR inhibitors in this setting. When appropriate, techniques and cut-offs will be standardized to determine the most practical, efficient, and robust biomarkers able to discriminate responders versus non-responders to chemotherapy+erlotinib. These biomarkers (herein referred to as erlotinib associated biomarkers [EAB]) will be CLIA certified (when appropriate) and incorporated into stage II. During stage II, patients will be adaptively randomized to the control or experimental arms according to their EAB status.

All patients randomized will be followed until the first post-operative, protocol-defined clinic visit. After that, clinical data up until the date of death will be obtained through chart review or by contacting the patients and/or their families. A schematic diagram of the study design is shown in **Figure 3–1**.

Figure 3–1: Study Schematic



Patients will be stratified by the following factors and randomized to Arm A or Arm B:

- Nodal staging (N0/N1 versus N2/N3). The nodal staging will be defined by the best available information at the time of randomization. For example, patients will not be required to undergo pathologic staging with neck lymph node biopsies prior to treatment, but if pathologic staging is available, the information will be combined to imaging and clinical data to obtain the most accurate stage.

3.1

Treatment Plan and Regimen

3.1.1 Treatment Plan

After assessment of eligibility and stratification factors, patients will be randomized to:

Arm A: Chemotherapy (up to 3 cycles) with erlotinib followed by daily erlotinib; or

Arm B: Chemotherapy (up to 3 cycles) with placebo followed by daily placebo

Use of cisplatin or carboplatin will be per the investigator's choice.

In both arms, three cycles of chemotherapy are planned. Patients may receive less than the planned number of chemotherapy cycles at the investigator's discretion (e.g. due to intolerable toxicities or achievement of maximal treatment benefit) – in such cases, the reason for premature chemotherapy discontinuation should be documented in the chart.

Erlotinib or placebo will be administered daily from day 1, cycle 1 until the day prior to surgery (including the day prior to surgery). Treatment should preferably start within 14 days of randomization.

Body surface area (BSA) for chemotherapy dose calculation will be determined according the following formula:

BSA (m^2) = [height (cm) x weight (kg) ÷ 3600] ^{½}

The actual body weight will be used for BSA calculation, but the investigators will consider using adjusted or ideal body weight if the BSA exceeds 2.0 m^2. BSA should be recalculated prior to the start of every cycle of therapy.

The dose of carboplatin to be administered will be calculated based on the patient's actual body weight and the AUC dosing, using the Calvert formula. However, investigators will consider using adjusted or ideal body weight if the BSA exceeds 2.0 m^2. The creatinine clearance(CrCl) / glomerular filtration rate (GFR) used to calculate the carboplatin dose will be estimated, based on serum creatinine, using the Cockcroft-Gault formula:

For males:

Cr Cl (mL/min) = [(140-age) x (weight in kg)] ÷ [72 x serum creatinine in mg/dL]

For females:

Cr Cl (mL/min) = [(140-age) x (weight in kg) x 0.85] ÷ [72 x serum creatinine in mg/dL]

Carboplatin dosing, using the Calvert formula, is often based upon a calculated creatinine clearance using serum creatinine as a surrogate for renal function. Several assays are available to measure serum creatinine. In the United States and many parts of the world, most laboratories use methods that are standardized against reference material in which the creatinine value has been assigned by Isotope Dilution Mass Spectrometry (IDMS). Since 31 December 2010, all clinical laboratories in the United States have used creatinine methods standardized relative to the IDMS reference material.

The recalibration of serum creatinine measurements against the IDMS reference material may result in slight differences in reported serum creatinine levels in the low range of normal. If the total carboplatin dose is calculated based on an estimated GFR using an IDMS-standardized serum creatinine and the Calvert formula, carboplatin dosing could be higher than if the GFR had been directly measured, and could result in increased toxicity.

If creatinine is determined by a method standardized to the IDMS reference material, the estimated GFR used in the Calvert formula to calculate area under the curve (AUC)-based dosing should not exceed 125 mL/min for patients who have not begun therapy.

Calvert Formula

Total carboplatin dose (mg) = (target AUC) x (GFR + 25)

Maximum carboplatin dose (mg) = target AUC 6 (mg.min/mL) x (125 + 25) = 6 x 150 mL/min = 900 mg

Surgery will be performed preferably no earlier than 3 weeks and no later than 6 weeks after the last chemotherapy (cisplatin/carboplatin, docetaxel) administration.

Post-operative (chemo)radiation therapy will be delivered according to institutional guidelines and the best judgment of the treating physicians, preferably within 6 weeks of surgical resection. While not formally required per protocol, it is strongly suggested that the following principles of (chemo)radiation therapy be followed:

- Primary tumor and involved nodal stations to receive 60-66 Gy (2 Gy/fraction)
- Uninvolved nodal stations to receive 44-64 Gy (1.6-2.0 Gy fraction)
- Concurrent chemotherapy to be added to post-operative radiation therapy in patients with positive margins or extra-capsular nodal spread. Cisplatin 100 mg/m^2 on days every 3 weeks for 2-3 doses or cisplatin 40 mg/m^2/week for 6-7 doses are preferred regimens. Carboplatin AUC 2/week for 6-7 doses may be used, less preferably.

Table 3–1: Schedule of Study Drug Administration

Treatment Arm	Agent(s)	Starting Dose	Route	Schedule
A	Docetaxel	75 mg/m^2	IV	Day 1 q 21 days ± 3 days [a]
	Cisplatin	75 mg/m^2	IV	Day 1 q 21 days ± 3 days [a]
	or carboplatin	AUC 6 mg.min/ml	IV	
	Erlotinib	150 mg/day	PO	Continuously [b]
B	Docetaxel	75 mg/m^2	IV	Day 1 q 21 days ± 3 days [a]
	Cisplatin	75 mg/m^2	IV	Day 1q 21 days ± 3 days [a]
	or carboplatin	AUC 6 mg.min/ml	IV	
	Placebo	150 mg/day	PO	Continuously [b]

[a] For a maximum of 3 cycles.

[b] Until the day prior to surgery (including the day prior to surgery).
If the patient completes < 3 cycles of chemotherapy with a response (CR or PR) or stable disease but cannot continue chemotherapy (eg, due to toxicity), daily erlotinib (in Arm A) or daily placebo (in Arm B), at the most recent dose, will be continued until the day prior to surgery (including the day prior to surgery)

3.1.2 Dose Modifications for Chemotherapy

Toxicities will be graded by using the NCI CTCAE version 4.0. Refer to the following website for the CTCAE manual or the CTCAE document:

http://ctep.cancer.gov

The dose modifications outlined below are considered general guidelines. The investigator should use his or her best judgment when determining treatment interruptions and dose modifications. For example, some grade 2 non-hematologic toxicities may require treatment delays and/or dose reductions, and some grade 3 or 4 organ toxicities (e.g., hepatic, renal, cardiac, central nervous system) may require a permanent treatment discontinuation. If one chemotherapy agent (docetaxel or cisplatin/carboplatin) needs to be discontinued, the other chemotherapy agent (cisplatin/carboplatin or docetaxel) may be continued. Docetaxel or cisplatin/carboplatin dose will not be re-escalated once it has been reduced for toxicity.

3.1.2.1 Dose Modifications for Docetaxel

The dose of docetaxel will be reduced according to the following guidelines.

Thrombocytopenia

- If grade 4 thrombocytopenia occurs, the dose of docetaxel will be reduced by 25% for subsequent cycles. If grade 4 thrombocytopenia persists despite dose reduction, docetaxel treatment will be discontinued.

Neutropenia

The dose of docetaxel will be reduced for the following neutropenic conditions as outlined in **Table 3–2:**

- Grade 4 neutropenia lasting $\geq$ 7 days
- Grade 3 or 4 febrile neutropenia

Table 3–2: Docetaxel Dose Modifications for Neutropenia

Dose Description	Docetaxel Dose (mg/m^2)
starting dose	75 mg/m^2
1st dose reduction due to neutropenia (patients not receiving prophylactic growth factor support)	75 mg/m^2 add growth factor support
1st dose reduction due to neutropenia (patients receiving prophylactic growth factor support)	65 mg/m^2 continue growth factor support
2nd dose reduction due to neutropenia	50 mg/m^2 continue growth factor support

If grade 4 neutropenia or grade 3-4 febrile neutropenia persists despite dose reduction to 50 mg/m^2 with growth factor support, docetaxel treatment will be discontinued.

Hepatic Dysfunction

The dose of docetaxel will be reduced for abnormal liver function test as outlined in **Table 3–3**.

Table 3–3: Docetaxel Dose Modifications for Abnormal Liver Function

Total Bilirubin		Alkaline Phosphatase		SGOT or SGPT	Action
> ULN	**OR**	> 5 x ULN	**OR**	> 5 x ULN	Delay treatment ≤ 3 weeks until recovery. If recovered*, reduce docetaxel dose by 25%. If not recovered in ≤ 3 weeks, discontinue docetaxel.
≤ ULN	**AND**	≤ 5 x ULN	**AND**	1.6 – 5 x ULN	Reduce docetaxel dose by 25%

*Bilirubin ≤ ULN ***and*** alkaline phosphatase ≤ 5 x ULN ***and*** SGOT or SGPT ≤ 5 x ULN

Note: a maximum of two dose reductions per patient are allowed. If liver toxicities persist despite two dose reductions, docetaxel treatment will be discontinued. Dose reductions triggered by elevated bilirubin levels will not be implemented in patients with Gilbert's syndrome.

Stomatitis

- If grade 3 or 4 stomatitis occurs, the dose of docetaxel will be reduced 25% for subsequent cycles. If grade 3 or 4 stomatitis persists despite dose reduction, docetaxel treatment will be discontinued.

Peripheral Neuropathy

- If grade 3, or clinically significant grade 2 (as judged by the investigator) neuropathy occurs, the dose of docetaxel will be reduced by 25%. If grade 3, or clinically significant grade 2 (as judged by the investigator) neuropathy persists despite two dose reductions, docetaxel treatment will be discontinued.
- If grade 4 neuropathy occurs, docetaxel treatment will be discontinued.

Hypersensitivity Reactions

- There are no dose reductions for hypersensitivity reactions. Management of acute hypersensitivity reaction should follow the Institutional guidelines. Re-treatment with docetaxel will be allowed at the investigator's discretion.
- If grade 4 hypersensitivity reactions occur, docetaxel treatment will be discontinued.

Fluid Retention

- There are no dose reductions for fluid retention.

Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to Taxotere are listed below.

- Triamterene/hydrochlorothiazide one capsule (37.5 mg / 25 mg) po qd up to tid.
- Furosemide 40 mg po daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
- If after a two-week trial, furosemide 40 mg po qd is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment."

Other Non-Hematologic Toxicities

- If grade 3 or 4 clinically significant (as judged by the treating physician) non-hematoligc toxicities occur (other than those listed above), docetaxel treatment will be withheld until the toxicity has resolved to $\leq$ grade 1 and then reinstituted (if medically appropriate) at a 25% dose reduction. If a grade 3 or 4 clinically significant toxicity recurs despite two dose reductions, docetaxel treatment will be discontinued.
- If treatment is withheld for > 3 weeks due to a grade 3 or 4 toxicity, docetaxel treatment will be discontinued.

3.1.2.2 Dose Modifications for Cisplatin or Carboplatin

If any grade 3 or 4 toxicity occurs that is consistent with the cisplatin or carboplatin side effect profile (e.g., renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range [4000 to 8000 Hz],

nausea and vomiting, hyperuricemia, mild to moderate anemia, and irreversible peripheral neuropathy), the dose of cisplatin or carboplatin will be reduced as outlined in **Table 3–4**. Additionally, the investigator may choose to switch from cisplatin to carboplatin (or vice versa) during cycles 2 to 6 as an attempt to minimize the incidence or severity of platinum-related toxicities.

Table 3–4: Cisplatin/Carboplatin Dose Modifications

Dose Level	Cisplatin Dose (mg/m^2)	Carboplatin Dose (AUC, mg.min/ml)
0 Starting Dose	75 mg/m^2	6
-1	60 mg/m^2	5
-2	50 mg/m^2	4

If toxicities persist despite two dose reductions, cisplatin or carboplatin treatment will be discontinued.

3.1.2.3 Re-treatment Criteria for Docetaxel and Cisplatin or Carboplatin

Prior to receiving any dose of docetaxel and cisplatin / carboplatin, patients must have an ANC $\geq$ 1.5 x 10^9/L and a platelet count $\geq$ 100 x 10^9/L (see **Table 3–5**). If the ANC is < 1.5 x 10^9/L and platelet count is < 100 x 10^9/L, the treatment should be delayed for $\leq$ 3 weeks. If the patient is unable to be treated after a 3-week delay, the patient will be discontinued from chemotherapy. Patients who have discontinued chemotherapy will be allowed to continue on daily, single-agent erlotinib or placebo as described in **Section 3.1.1**.

Table 3–5: Re-treatment Criteria for Subsequent Cycles of Docetaxel and Cisplatin / Carboplatin

DAY 1 COUNTS AND MAJOR ORGAN TOXICITY GRADING			
Neutrophils ($\times 10^9$/L)		**Platelets ($\times 10^9$/L)**	**Timing**
$\geq$ 1.5	**AND**	$\geq$ 100	Treat on time
< 1.5	**OR**	< 100	Delay until recovery*
* If patient does not recover in $\leq$ 3 weeks, chemotherapy will be discontinued. Patients will be allowed to continue on daily, single-agent erlotinib or placebo as described in **Section 3.1.1**			

3.1.3 Dose Modifications for Erlotinib or Placebo

3.1.3.1 Erlotinib or Placebo Dose Reductions and Re-Escalation

Erlotinib doses may be reduced and/or delayed for toxicities (see **Table 3–7**). If a patient experiences several toxicities, dose adjustments are to be made based on the greatest degree of toxicity. In the event of any toxicity requiring erlotinib dose reduction, the daily dose of erlotinib will be decreased according to the schedule below (**Table 3–6**). If significant toxicity is still apparent, the dose may be reduced a second time.

Table 3–6: Dose Modifications for Erlotinib

Erlotinib Dose	First Reduction	Second Reduction
150 mg/day	100 mg/day	50 mg/day

Patients who require a dose reduction must be evaluated until the toxicity stabilizes or improves. Doses that have been reduced one dose level for toxicity may be re-escalated to the previous 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 two dose levels for toxicity may only be re-escalated to the previous dose level (i.e., dose level at first reduction) and 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 two dose levels for toxicity may not be re-escalated to starting dose level. Any patient who fails to tolerate treatment at 50 mg/day will be discontinued from erlotinib or placebo. Patients will be allowed to continue receiving chemotherapy, until the planned numbered of chemotherapy cycles has been reached.

Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity (see **Table 3–7**). Patients experiencing toxicities that require a delay in erlotinib dosing for > 21 days will be discontinued from the study.

Treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with erlotinib. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pre-treatment values outside normal range.

Table 3–7: Dose Reduction Criteria for Erlotinib-related Toxicities

Toxicity (NCI CTCAE v4.0)	Dose Modification [a]
Diarrhea	
Grade 1 or 2	None. Initiate therapy with loperamide (**Section 5.6.1.2**)
Grade 3 [b] or 4 [b]	Interrupt study drug until resolution to ≤ grade 2 and then restart 1 dose level lower.
Rash	
Grade 1	None
Grade 2 [c]	None. If rash persists and is intolerable over 10 – 14 days, then reduce by 1 dose level and initiate treatment as outlined in **Section 5.6.1.2.**
Grade 3 [b, c]	Reduce by 1 dose level. If rash persists or worsens over 10 – 14 days, then interrupt study drug until resolution to ≤ grade 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue study drug.
Interstitial Lung Disease	
Any Grade	If ILD is suspected, study drug should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, study drug should be discontinued permanently and appropriate treatment instituted as necessary.
Other Toxicities	
Grade 1 or 2	None
Grade 3 [b, d]	Interrupt study drug until resolution to ≤ grade 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue study drug.

[a] Doses that have been reduced one dose level for toxicity may be re-escalated to the previous 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 two dose levels for toxicity may only be re-escalated to the previous dose level (ie, dose level at first reduction) and 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 two or more dose levels for toxicity may not be re-escalated to starting dose level. Any patient who fails to tolerate treatment at 50 mg/day will be discontinued from the study. Patients will be allowed to continue receiving chemotherapy, until the planned numbered of chemotherapy cycles has been reached.

[b] If the event does not resolve to ≤ grade 2 within 21 days, study drug will be discontinued. Appropriate measures should be taken to intensively treat dehydration. Since there have been rare reports of hypokalemia and acute renal failure (including fatalities) secondary to severe dehydration, renal function and serum electrolytes (including potassium) should be monitored in this setting.

[c] Doxycycline and minocycline are often used to treat grade 2 or 3 rash even if there is no clear evidence for superinfection. Rash should not be classified as grade 3 solely on the basis of use of antibiotics, unless there is strong suspicion for superinfection in the opinion of the investigator.

[d] Only if ≥ 2 grade level change from baseline.

3.1.3.2 Erlotinib or Placebo Dose Interruptions

Patients who have a continuous interruption of erlotinib or placebo dosing for $\leq$ 21 consecutive days may re-start erlotinib or placebo at the appropriate dose, provided toxicities have improved as outlined above.

Patients who have a continuous interruption of erlotinib or placebo dosing for > 21 consecutive days are not allowed to re-start erlotinib or placebo.

4 PATIENT POPULATION

Patients with suspected or histologically confirmed HNSCC of the oral cavity, stage III, IVA or IVB (according to the AJCC 7th edition), who have an ECOG performance status of 0-2, will be enrolled. Patients with a suspected lesion may be enrolled and a baseline biopsy will be obtained as part of the study. If squamous cell histology is not confirmed, patients will be discontinued from the study.

Questions about eligibility criteria should be addressed **PRIOR** to randomization. The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to assure that patients who enter this study are medically appropriate candidates for this therapy.

4.1 Inclusion Criteria

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

1. Suspected or histologically/citologically confirmed HNSCC of the oral cavity, stage III, IVA or IVB (according to the AJCC 7th edition). Patients with a suspected lesion may be enrolled and a baseline biopsy will be obtained as part of the study. If squamous cell histology is not confirmed, patients will be discontinued from the study.
2. Patients must have surgically resectable disease, in the opinion of the treating physician
3. Age $\geq$ 18 years.
4. ECOG PS $\leq$ 2 (Appendix C)
5. Adequate bone marrow, hepatic and renal function defined by:
    a. ANC $\geq$ 1.5 x 10^9/L;
    b. Platelet count $\geq$ 100 x 10^9/L;
    c. ALT (SGPT) $\leq$ 1.5 x upper limit of normal (ULN);
    d. Total bilirubin $\leq$ ULN (patient's with Gilbert's syndrome are eligible, even if total bilirubin is > ULN);
    e. Alkaline phosphatase $\leq$ 2.5 x ULN;
    f. Serum creatinine $\leq$ 1.5 x ULN.
6. Patients with reproductive potential (e.g., females menopausal for less than 1 year and not surgically sterilized) must practice effective contraceptive measures for the duration of study drug therapy and for at least 30 days after completion of study drug therapy. Female patients of childbearing potential must provide a negative pregnancy test (serum or urine) $\leq$ 14 days prior to treatment initiation.

7. Written informed consent to participate in the study according to the investigational review board (IRB).

4.2 Exclusion Criteria

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

1. Histology other than squamous cell carcinoma.
2. Primary sites other than oral cavity.
3. Prior chemotherapy or biologic therapy for the same HNSCC. Prior chemotherapy or biologic therapy for a different previous HNSCC is allowed
4. History of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug (e.g., Crohn's disease, ulcerative colitis). Patients requiring feeding tubes are permitted
5. Other active solid malignancies within 2 years prior to randomization, except for basal cell or squamous cell skin cancer or in situ cervical or breast cancer or superficial melanoma.
6. Serious underlying medical condition which would impair the ability of the patient to receive protocol treatment, in the opinion of the treating physician.
7. History of allergic reactions to compounds of similar chemical composition to the study drugs (docetaxel, cisplatin, carboplatin, erlotinib or their excipients), or other drugs formulated with polysorbate 80.
8. Any concurrent anticancer therapy, excluding hormonal therapy for prostate or breast cancer.
9. Women who are pregnant or breast-feeding and women or men not practicing effective birth control.

5 STUDY DRUG(S) AND CONCOMITANT MEDICATIONS

The term “study drug” refers to the chemotherapy (docetaxel and cisplatin / carboplatin) and to erlotinib. The patient is considered “on treatment” until all study drug is discontinued.

5.1 Description, Handling and Administration of Docetaxel

MDACC will use its own commercial supply of docetaxel in this study. Docetaxel will be prepared and administered according to local practice and in accordance with the most recent Package Inserts/Data Sheets.

Pre-medications: To reduce the severity of fluid retention and hypersensitivity reactions, all patients will be pre-medicated with corticosteroids, such as oral dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to docetaxel administration. Considerations for modification of the corticosteroid regimen (including schedule and dose reductions) should be made in patients receiving the prophylactic anti-emetics fosaprepitant or aprepitant.

5.2 Description, Handling and Administration of Cisplatin / Carboplatin

MDACC will use its own commercial supply of cisplatin or carboplatin in this study. Cisplatin or carboplatin will be prepared and administered according to local practice and in accordance with the most recent Package Inserts/Data Sheets.

Pre-medications: All patients will receive anti-emetics and/or appropriate hydration prior to and after cisplatin or carboplatin administration according to current institutional guidelines.

5.3 Description, Handling and Administration of Erlotinib or Placebo

5.3.1 Formulation of Erlotinib

Astellas Pharma/OSI Pharmaceuticals will supply tablets containing erlotinib hydrochloride equivalent to 150 mg, 100 mg, and 25 mg of erlotinib (Arm A) or matching placebo (Arm B). All tablets are round, white, film-coated, and bi-convex with no imprint. Additional information can be found in the Erlotinib Investigator’s Brochure.

5.3.2 Packaging and Labeling of Erlotinib or Placebo

Erlotinib or placebo will be supplied in blue-white, high-density, polyethylene bottles of 30 tablets each. If the dose has been modified to 50mg, then two bottles with 30 tablets of 25mg each of erlotinib (Arm A) or matching placebo (Arm B) will be supplied. The bottles will have a tamper-evident seal and a child-resistant cap.

5.3.3 Storage and Handling of Erlotinib or Placebo

Erlotinib or placebo drug tablets should be stored between 15°C and 30°C (59°F and 86°F).

5.3.4 Administration of Erlotinib or Placebo

Erlotinib (Arm A) or placebo (Arm B) tablets should be taken at approximately the same time each day, preferably in the morning. Each dose is to be taken with up to 200 mL (~ 1 cup or 8 oz) of water, and should be taken on an empty stomach either 1 hour before or 2 hours after a meal or medications, including vitamins and other supplements. Any consumption of grapefruit and grapefruit juice should be avoided while on erlotinib treatment (see **Section 5.6.3**).

The entire dose must be taken at one time. If the patient vomits after taking the tablet(s), the dose should be replaced only if the tablet(s) can actually be seen and counted.

If necessary, patients may receive erlotinib or placebo via a feeding tube. The suggested method of preparation and administration is as follows: the tablet is placed in approximately 6 ounces of water, and allowed to dissolve (usually for 15-20 minutes); once dissolved the solution is then administered via the feeding tube, followed by a free water flush.

5.4 Drug Accountability

A drug accountability log for erlotinib (Arm A) or placebo (Arm B) will be maintained. The information contained on the log should be sufficient to comply with applicable GCP regulations. Drug accountability log information may include, but is not limited to, the following: number of bottles and date the study drug was received, number of bottles dispensed to each patient (including bottle number, date dispensed/returned, patient identifier information, protocol number, dose, and lot/batch number), quantity of tablets returned by the patient, current balance, and the initials of the person who recorded the accountability log information. At the time of study closure, both the unused, used, and

expired study drug will be destroyed by MD Anderson's Investigational Pharmacy Services per MD Anderson's institutional SOPs. Astellas Pharma/OSI Pharmaceuticals will be provided with the documentation of the drug destruction upon request.

5.5 Treatment Compliance

Compliance of erlotinib (Arm A) or placebo (Arm B) will be assessed by counting tablets at the scheduled patient visits. In addition, pill diaries will be used by the patient and reviewed by the research nurse to assess compliance during the patient's scheduled visits. Data regarding missed or modified doses will be recorded in the patient's chart.

5.6 Concomitant Medications

All concomitant medications will be recorded on the patient's medical record.

5.6.1 Permitted Concomitant Medications

5.6.1.1 Pre-medications for Chemotherapy

Standard pre- and post-medications will be administered with docetaxel and cisplatin / carboplatin infusions (see **Section 5.1** and **Section 5.2**).

5.6.1.2 Anti-diarrhea and Anti-rash Therapies

Skin rash or 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. Patients should be told that skin toxicity is to be expected during treatment with erlotinib. Skin toxicity may take the form of dry skin, rash, acneiform eruption, or hair or nail changes. Prophylactic treatment of the skin may prevent or reduce skin toxicity. The patient should be encouraged to use an alcohol-free, emollient cream applied twice a day to the entire body as soon as the patient starts therapy with erlotinib. Creams and ointments are recommended because they have a greater ability to retain moisture than lotions. Examples of suitable emollient creams include: Neutrogena® Norwegian formula, SARNA® Ultra, Vanicream™, Aveeno® (fragrance-free formulation), and Eucerin® cream. Other over-the-counter aqueous creams or emulsifying ointments may also provide symptomatic benefit. Lotions should be avoided because they often contain alcohol, which will dry the skin. Patients should also be encouraged to use a titanium dioxide or zinc oxide-based sunscreen product applied to sun-exposed areas twice per day.

Patients who develop skin toxicity and are symptomatic should be treated with topical therapy such as hydrocortisone cream or clindamycin gel. If needed, oral minocycline or oral doxycycline may be combined with the topical therapy. For more severe rash, oral corticosteroids may be beneficial.[21] Patients who fail to respond to these measures may have the dose of erlotinib interrupted or reduced. A suggested algorithm for treatment of erlotinib-related skin toxicities is presented in **Table 5-1**.

Table 5-1: Treatment of Erlotinib-Related Skin Toxicities

Toxicity Grade	Macular Rash	Pustular Rash	Dry Skin	Pruritus	Ulcerative lesions
1	Hydrocortisone topical cream/ lotion	Clindamycin gel (for isolated lesions)/ lotion (for scattered lesions)	-	-	-
2	Oral methylprednisolone (if > 2 body regions) Topical hydrocortisone if <2 body regions	Minocycline or doxycycline 100 mg po BID for 10-14 days	Emollient applied BID	Topical antihistamine or diphenhydramine 25-50 mg po q6h prn	-
3	Oral methylprednisolone	Minocycline or doxycycline 100 mg po BID for 10-14 days	Emollient applied BID	Diphenhydramine 25-50 mg po q6h or hydroxyzine 25-50 mg po q6h prn	Silver sulfadiazine ointment
	Dermatology consult				
4	Discontinue therapy				

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.

Anti-diarrheal medications may be introduced if symptoms occur. Previous trials have shown that the frequency and severity of diarrhea rarely hindered administration of erlotinib and could be managed with loperamide (see **Table 3–7**). 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.

5.6.1.3 Anticoagulant Therapies

Concomitant treatment with warfarin or other coumarin-derived anticoagulants are permitted provided increased vigilance occurs with respect to monitoring their anticoagulation status. INR elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on erlotinib. For this study, patients taking warfarin or other coumarin-derived anticoagulants while on study drug should be monitored as clinically indicated for changes in prothrombin time or INR.

5.6.1.4 Hematopoietic Growth Factors

Prophylactic G-CSF support is strongly recommended and should be administered at least 24 hours after infusion of chemotherapy, beginning at cycle 1 and continued for the duration of treatment with chemotherapy. Treating physicians may discontinue G-CSF administration at cycles ≥ 2 provided that the patient did not have febrile neutropenia or grade 4 neutropenia lasting $\geq$ 7 days on previous cycles, and provided that the patient is experiencing adverse events associated with G-CSF administration.

5.6.1.5 Anti-emetic Therapy

Prophylactic anti-emetics may be administered at the discretion of the investigator.

5.6.2 Prohibited Concomitant Medications

5.6.2.1 Cytotoxic or Biological or Immune Response Modifiers

No other cytotoxic therapy, biological or immune response modifiers or other molecularly targeted therapies for the treatment of cancer may be administered to patients while they are on study drug, excluding hormonal treatment for breast and prostate cancer.

5.6.2.2 Other Investigational Drug Therapies

Patients should not receive any other investigational drugs with potential anti-neoplastic activity until disease progression has been documented.

5.6.3 Potential for Drug Interactions

Erlotinib is protein bound (92% to 95% in humans) and metabolized by hepatic cytochromes CYP3A4 and CYP1A2 and pulmonary cytochrome CYP1A1. Therefore, a potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 or CYP1A2 inhibitors/inducers (see Appendix D).

Substances that are potent inhibitors of CYP3A4 activity (e.g., ketoconazole) decrease erlotinib metabolism and increase erlotinib plasma concentrations. This increase may be clinically relevant as adverse experiences are related to dose and exposure. Therefore, for this study, such agents should be avoided and, if that is not possible, caution should be used when administering CYP3A4 inhibitors to patients who are on study drug.

Substances that are potent inducers of CYP3A4 activity (e.g., rifampin, phenytoin) increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. This decrease in exposure may be clinically relevant, as preclinical studies suggest that higher concentrations are more efficacious in in vivo animal tumor models. However, the relationship between exposure and efficacy in cancer patients has not been adequately studied. Therefore, for this study, such agents should be avoided, and if that is not possible, caution should be used when administering CYP3A4 inducers to patients who are on study drug. For more information, refer to the erlotinib Investigator's Brochure.

In vitro studies have shown that the metabolism of docetaxel may also be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving docetaxel as there is a potential for a significant interaction.

As mentioned in **Section 5.6.1.3**, INR elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on erlotinib. During this study, patients taking warfarin or other coumarin-derived anticoagulants should be monitored as clinically indicated for changes in prothrombin time or INR.

Erlotinib clearance can be induced by smoking via CYP1A2 induction. Smokers should be advised to stop smoking while taking erlotinib, as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking.

Aqueous solubility of erlotinib is dependent on pH with increased solubility at a pH less than 5; maximal solubility occurs at a pH of approximately 2. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure (AUC) and maximum concentration (C_{max}) by 46% and 61%, respectively. There was no change in T_{max} or half-life. Therefore, drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of

erlotinib when co-administered with such agents is not likely to compensate for the loss of exposure. While the concomitant use of erlotinib and proton pump inhibitors is not forbidden during this study, patients will be advised to avoid medications that decrease stomach acid while participating on this study [e.g. Zantac® (ranitidine), Pepcid® (famotidine), Tagamet® (cimetidine), Protonix® (pantoprazole), Nexium® (esomeprazole), Prilosec® (omeprazole), Prevacid® (pantoprazole), or Aciphex® (rabeprazole)]. Short-acting antacids (e.g., Tums®, Maalox®, Mylanta®, Rolaids®) may be taken while on study, preferably more than 2 hours before or after the dose of erlotinib or placebo.

Grapefruit juice is a CYP3A4 inhibitor that interferes with the metabolism of erlotinib. Therefore, consumption of grapefruit or grapefruit juice should be avoided during erlotinib treatment.

5.6.4 Ophthalmologic Considerations

Patients with dry eyes should be advised to use an ocular lubricant. Patients who continue to wear contact lenses may have an increased risk of ocular adverse events (e.g., keratitis). The decision to continue to wear contact lenses should be discussed with the patient's treating oncologist and ophthalmologist prior to the patient going on study.

5.6.5 Unblinding Procedures

Un-blinding of single cases by the sponsor and/or investigator will only be performed if relevant for the safety of the participant. In emergency situations, the investigator would contact the sponsor, who would contact the study statistician and the investigational pharmacy to obtain immediate blinding information for the participant. The sponsor would then pass this information on to the investigator to enable the participant to be treated. In non-emergency situations, the same procedures would apply, however the study statistician and the study sponsor will discuss and evaluate the request, then, would be responsible for making the decision of whether or not to un-blind. Additionally, Dr. Agueda Cohen, Medical Monitor and the Clinical Research Monitor at the IND Office will also be notified in writing when un-blinding occurs.

Un-blinding of all participants will occur at the end of study, whereby the sponsor and investigators will be provided with a list containing data on which arms each of his/her patients were randomized to.

6 STUDY PROCEDURES

Patients may be accrued to and treated on this study at M. D. Anderson Cancer Center, including M. D. Anderson's Regional Care Centers. The study procedures to be conducted for each patient enrolled in the study are detailed in the text that follows.

6.1 Patient Enrollment and Treatment Assignment

Before recruitment of patients into the study, written IRB approval of the protocol, informed consent forms, and any additional patient information must be obtained. The investigator will maintain a patient log for all screened (including patients that failed screening) and randomized patients. Study-related procedures must not commence before obtaining consent. However, results from assessments performed before obtaining informed consent that are considered "routine standard of care" (e.g., laboratory results, CT scans, etc.) may be used to determine eligibility.

The physician in charge of the patient is responsible for verifying that the patient is eligible before requesting randomization. If any of the inclusion criteria are not met or any of the exclusion criteria are met, the patient should not be enrolled.

Randomization will be performed via a centralized, web-based randomization system. Patients who are randomized will be assigned to a treatment arm and given a unique patient number by the centralized, web-based system. Once enrolled in the study, the patient will only be identified by initials and the assigned patient number.

Patients will start treatment preferably within 14 days of randomization.

6.2 Baseline Assessments

Patients will be screened for the study according to the Baseline Assessments as outlined in **Table 6–1**.

Table 6–1: Baseline Assessments

Investigations		Timing
History and Physical Exam including:	• Treatment history • Medical history • Smoking history • Height and weight • Vital signs • ECOG PS • TNM stage	Within 14 days prior to treatment initiation
Current Smoking Status and Tobacco Use	• Assessment of patient's current smoking status and tobacco use	Within 14 days prior to randomization
Symptoms & Toxicities	• Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v4.0	Within 14 days prior to treatment initiation
Concomitant Medications	• Documentation of concomitant medications	Within 14 days prior to treatment initiation
Quality of Life	• FACT-H&N	Within 14 days prior to treatment initiation
Hematology	• CBC with hemoglobin, platelets, and WBC with differential	Within 14 days prior to treatment initiation
Biochemistry	• Albumin • Alkaline phosphatase • Total bilirubin • BUN • Creatinine • Glucose • LDH • Potassium • SGOT (AST) • SGPT (ALT) • Sodium • Magnesium	Within 14 days prior to treatment initiation
Pregnancy Test	• Urine or serum (for women of childbearing potential only)	Within 14 days prior to treatment initiation
Radiology	• CT or MRI scans of the head and neck • Additional imaging studies as clinically indicated • Optional imaging studies	Within 30 days prior to treatment initiation
Tumor Tissue Collection for Biomarkers	• A biopsy of primary lesion for biomarker analysis	Within 30 days prior to randomization
Blood-based biomarkers	• Blood sample	Within 30 days prior to treatment initiation

6.3 Study Assessments

6.3.1 Assessment During Chemotherapy

Patients in each arm will be evaluated prior to chemotherapy cycles according to the assessments outlined in **Table 6–2**.

Table 6–2: Assessments During Chemotherapy (All Arms)

Investigations			Timing
Physical Exam Including:	• BSA • Vital signs		Within 7 days prior to cycles 2-3, and at least 14 days after the last dose of chemotherapy
Current Smoking Status and Tobacco Use[1]	• Assessment of patient's current smoking status and tobacco use		Within 7 days prior to cycles 2-3, and at least 14 days after the last dose of chemotherapy
Hematology	• CBC with hemoglobin, platelets, and WBC with differential		Within 7 days prior to cycles 2-3, and at least 14 days after the last dose of chemotherapy
Biochemistry[1]	• Albumin • Alkaline phosphatase • Total bilirubin • BUN • Creatinine	• Glucose • LDH • Potassium • SGOT (AST) • SGPT (ALT) • Sodium • Magnesium	Within 7 days prior to cycles 2-3, and at least 14 days after the last dose of chemotherapy
Pregnancy Test	• Urine or serum (for women of childbearing potential only)		If/when clinically indicated
Radiology [1]	• CT or MRI scans of the head and neck • Additional imaging studies as clinically indicated • Optional imaging studies		At least 14 days after the last dose of chemotherapy
Symptoms & Toxicities	• Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v4.0		On an ongoing basis throughout the study until the final study visit
Concomitant Medications	• Documentation of concomitant medications		On an ongoing basis throughout the study until the final study visit
Quality of Life[1]	• FACT-H&N		At least 14 days after the last dose of chemotherapy
Blood-based biomarkers[1]	• Blood sample		At least 14 days after the last dose of chemotherapy
Erlotinib PK[1]	• Blood sample		At least 14 days after the last dose of chemotherapy
Erlotinib or Placebo Treatment Compliance	• Count tablets and record findings		At each clinic visit
[1] If information / studies have already been obtained but chemotherapy is delayed for any reason, repeated studies are not necessary prior to next cycle of chemotherapy.			

6.3.2 Assessments at Surgery

After completing chemotherapy, patients will undergo surgical resection. Evaluations will be performed according to Table 6-3.

Table 6–3: Assessments at Surgery

Investigations		Timing
Surgical procedure	• Title of operation	Through chart review
Tumor Tissue Collection	• pTNM • Pathologic response • Percentage of viable tumor cells • Status of resection margins • Number of lymph nodes removed at each level • Number of lymph nodes positive for cancer at each level • Evaluation of extra-capsular nodal spread • Evaluation of peri-neural invasion • Evaluation of vascular invasion • Biomarker evaluation	As information becomes available

6.3.3 End of Treatment Assessments

For all patients, the End of Treatment Visit will occur approximately within 8 weeks after surgery, and preferably before initiating post-operative radiation therapy. Patients will be evaluated according to the assessments outlined in **Table 6–4**. For patients that do not undergo surgery, an end of treatment assessment will not be performed.

Table 6–4: End of Treatment Assessments

Investigations		Timing
Physical Exam Including:	• Vital Signs	Approximately within 8 weeks after surgery
Blood-based biomarkers	• Blood sample	Approximately within 8 weeks after surgery
Erlotinib PK	• Blood sample	Approximately within 8 weeks after surgery
Pregnancy Test	• Urine or serum (for women of childbearing potential only)	If/when clinically indicated
Symptoms & Toxicities	• Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v4.0 • Retrospective evaluation of any unexpected surgical complications	Approximately within 8 weeks after surgery
Quality of Life	• FACT-H&N	Approximately within 8 weeks after surgery

6.4 Descriptions of Study Assessments

6.4.1 Smoking History

The following definitions of cigarette smoking status will be used to categorize and stratify patients in the study:

- **Current cigarette smoker:** has smoked > 100 cigarettes in entire lifetime and is either currently smoking or quit smoking < 1 week ago
- **Former cigarette smoker:** has smoked > 100 cigarettes in entire lifetime and quit smoking $\geq$ 1 week before randomization
- **Never smoker:** has smoked $\leq$ 100 cigarettes in entire lifetime and stopped or never smoked cigarettes

Tobacco use other than cigarette smoking will also be assessed according to **Tables 6-1** to **6-4**.

6.4.2 Performance Status

The performance status of all patients will be graded at scheduled intervals according to the ECOG PS scale.

6.4.3 Clinical Laboratory Tests

Clinical laboratory tests will be performed to assess eligibility for enrolment and will be repeated according to **Tables 6-1** to **6-4**.

Laboratory tests can be repeated more frequently, if clinically indicated.

6.4.4 Symptoms and Toxicity Assessment

The symptoms and adverse events of all patients will be graded at scheduled intervals according to the NCI CTCAE, v4.0. Patients will be monitored continuously throughout the study for the occurrence of adverse events. Planned medical interventions (e.g., planned surgical resection) will not be considered an adverse event. For the purpose of this study, adverse events that in the opinion of the treating investigator are related to planned surgical procedure (e.g., usual pain, usual bleeding, intra- or post-operative electrolyte imbalances and other clinically insignificant laboratory abnormalities) will not be captured and/or reported. Unexpected surgical complications will be retrospectively reviewed at the end of treatment assessments, as described in **Table 6-4**.

6.4.5 Radiology Assessments

CT or MRI scans of the head and neck will be obtained according to **Tables 6-1** to **6-4**. Additional methods may be performed at physician discretion.

Response and progression will be evaluated in the study using the international criteria proposed by the RECIST committee[22] (see Appendix E), and preferably by the same investigator or collaborator.

To ensure comparability, the baseline radiology/scans and subsequent radiology/scans to assess response should, preferably, be performed using identical techniques.

Patients enrolled to this study may also be offered optional participation in a separate IRB-approved protocol evaluating additional imaging modalities for HNSCC. An independent informed consent process will be followed for accrual to such protocol.

6.4.6 Quality of Life

Quality of life will be measured by the FACT-H&N quality of life questionnaire (see Appendix F). The patient should complete the questionnaire at scheduled intervals according to **Tables 6-1** to **6-4**.

6.4.7 Tumor Tissue Samples

Baseline tumor tissue samples from the primary tumor will be collected for histopathological examination and biomarkers. Samples will be obtained by an outpatient punch-biopsy or large-cup forceps biopsy performed under local anesthesia, preferably with a minimum of 4-5 mm diameter (which allows for the preparation of at least 30 slides). These specimens should be fixed in 10% formalin, preferably immediately and not more than 1 (one) hour after excision. Fixed biopsy samples will be processed for paraffin-embedding according to the Institutional Standard Operating Procedures. The paraffin blocks and slides should be labeled with the protocol number and the patient's unique study identification number and stored at room temperature. A portion of the specimen obtained (or a second biopsy) will also be embedded in optimal cutting temperature compound immediately after received and not more than 1 (one) hour after excision, frozen, and stored at -80 ^{o}C for future biomarker analysis. All samples stored at -80 ^{o}C should be placed in appropriate containers, labeled with the protocol number and the patient's unique study identification number.

Tumor tissue will also be obtained at surgical resection. The recommended procedure for obtaining the tissue specimens is as follows: the primary tumor should be identified on exam under anesthesia and at least 2 (two) large-cup forceps biopsies obtained prior to ligation of the tumor vessels, to avoid ischemia-induced activation of phosphatases. A portion of the tissue will be fixed in 10% formalin immediately after received and not more than 1 (one) hour after excision. Fixed biopsy samples will be processed for paraffin-embedding according to the Institutional Standard Operating Procedures. The paraffin blocks and slides should be labeled with the protocol number and the patient's unique study identification number and stored at room temperature. Another portion of the tumor specimen (preferably one sample ≥ 2 mm3 or 100 mg) will be embedded in optimal cutting temperature compound immediately after received and not more than 1 (one) hour after excision, frozen and stored at -80 ^{o}C for biomarker analysis. The remaining specimens resected during surgery will be used for routine histopathological diagnosis and will also be stored for future biomarker studies.

The surgical specimens will be evaluated for pathologic staging (pTNM) according to the AJCC 7th edition, pathologic response, quantification of percentage of viable tumor cells, status of resection margins, number of lymph nodes removed at each level, number of lymph nodes positive for cancer at each level, presence of extra- capsular nodal spread, peri-neural invasion and vascular invasion. To determine the pathologic response, specimens will be grossed and processed by the head and neck pathologist. The entire specimen measurement and the size of visible residual tumor will be documented. At least 1 block/1 cm of tumor will be submitted (average of 5-10 blocks/patient). All slides prepared from blocks taken from each specimen will be reviewed by the head and neck pathologist, as well as slides from each dissected lymph node.

Biomarkers to be evaluated in tumor tissue samples will include (but are not restricted to): EGFR, phospho-EGFR, IGF-1R, phospho-IGF-1R, IGF-2R, IGF-1, IGF-2, IGFBP-3, survivin, Ki-67, caspase-3, HIF-1 alpha, CD31, MMP-2, MMP-9, e-cadherin, gamma catenin, vimentin, fibronectin, p16, p53, markers of human papillomavirus infection, phosphorylation status of multiple kinases (using antibody arrays when appropriate), non-coding-RNA and messenger-RNA expression levels (using high-throughput microarray chips or sequencing), high-throughput genomic analysis (including genome sequencing and SNP analysis), high-throughput proteomic analysis, and other biomarkers that may emerge to be important related to the use of cisplatin/carboplatin, docetaxel and/or EGFR-targeted therapy.

6.4.8 Blood-based Biomarkers and Serum Pharmacokinetics

Blood will be collected, at scheduled intervals according to **Tables 6-1** to **6-4,** using three (3) EDTA (10 mL) Vaccutainer tubes for plasma and blood cells separation and storage. Samples for pharmacokinetics should preferably be obtained within 2 hours before the next erlotinib or placebo dose. Samples from the main campus will be forwarded to the core laboratory to be processed within one hour of collection. Samples from the Regional Care Centers (Katy, Sugarland, Bay Area, and Woodlands) will be collected and placed in ice-bags for delivery to the core laboratory by 3 PM on the day it is collected.

Sample processing: blood will be centrifuged in a standard clinical centrifuge at 2500 RPM at 4 ^{o}C for 10 minutes.

Plasma: Aliquots of plasma 1.5 – 2.0 mL should then be transferred into each cryovial, labeled with the protocol number and the patient's unique study identification number. Care must be taken not to collect the "cell layer – buffy coat" and to leaving a small portion of plasma behind for buffy coat collection. Plasma cryovials will be stored at -80 ^{o}C until analysis.

Buffy coat: From each Vaccutainer, carefully collect the buffy coat – cell layer and place into a cryovial x 3 vials - prelabeled with the protocol number and the patient's unique study identification number. These cryovials will be stored at -80 ^{o}C until analysis.

Blood-based biomarkers will include (but are not restricted to): a panel of 59 cytokine and angiogenic factors measured by available Luminex multiplex beads kits (EMD-Millipore 39-Plex for cytokines/chemokines, 17-Plex for angiogenic/growth factors, and Human CVD Biomarker Panel 1 and ELISA assays for osteopontin, free and total IGF-1 and IGF-2, IGFBP-3, insulin, peptide C, free fatty acids, triglycerides, fructosamine, high-throughput proteomic analysis, plasma circulating free-DNA, plasma miRNA, and high-throughput genomic analysis (including genome sequencing) and other biomarkers that may emerge to be important for to the use of cisplatin/carboplatin, docetaxel and/or EGFR-targeted therapy.

6.4.9 Tissue and Blood Sample Repository

As part of the study, a tissue and blood sample repository will be created. The objective of this tissue sample repository will be to provide material for future evaluations of other relevant biomarkers that may be associated with clinical outcomes. A written informed consent will be obtained from patients enrolled in this study so that these remaining samples may be analyzed in the future for biomarkers not described in this protocol. Banking of these remaining samples will be optional.

6.4.10 Long-Term Follow-Up

After the End of Treatment evaluation, information on additional oncologic treatment (including post-operative (chemo)radiation), time to disease progression/recurrence, sites of recurrence, development of second primary tumors, additional therapy for recurrence, long-term survival, and other relevant clinical data will be obtained.

Two years of long-term follow up is required. The trial is deemed completed after last subject completed trial planned treatment and two years of follow up, and primary trial report is finalized in publication format.

6.5 Assessments for Premature Discontinuation from Study

If a patient discontinues treatment early (see **Section 6.6**), every attempt should be made to keep the patient in the study and perform the required End of Treatment assessments (see **Section 6.3.3**) and Long-Term Follow-up Information (see **Section 6.4.10**).

6.6 Criteria for Treatment Discontinuation

Study medication should be discontinued in the following instances:

- Disease progression (patients with evidence of clinical or symptomatic benefit despite radiological progression may continue treatment with erlotinib until the day before surgery);
- Adverse event (see **Section 7.2**) either:
  - Resulting in death;
  - Requiring withdrawal from study; and/or
  - Fail to recover from hematological and/or nonhematological toxicity despite a dosing interruption of more than 21 days (see **Section 3.1**).
- Medical or ethical reasons, including noncompliance, following discussion between the investigator and the Principal Investigator;
- Patient's request (excluding adverse events).

Patients discontinued from treatment will remain on study and all attempts will be made to complete all assessments described in **Section** 0.

7 ADVERSE EVENTS

7.1 Safety Assessment

Assessments will consist of monitoring and recording of adverse events and serious adverse events, physical examination, measurement of protocol-specific laboratory variables and vital signs, as well as other tests deemed important for this protocol. The specific procedures and intervals for assessment are described in **Section** 0. Circumstances in which these assessments should be reported as adverse events are described in **Section 7.5 and 7.6**. All patients who have received at least one exposure to study drug will be evaluated for safety of the study drug.

7.2 Definition of Adverse Event

An adverse event or adverse experience is any untoward medical occurrence in a study patient who is administered a study drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug.

Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials will also be considered 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). For the purpose of this study, adverse events that in the opinion of the treating investigator are related to planned surgical procedure (e.g., usual pain, usual bleeding, intra- or post-operative electrolyte imbalances and other clinically insignificant laboratory abnormalities) will not be captured and/or reported.

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration should be considered pre-existing and should be documented in the chart.

An adverse event **does not** include:

- Relapse or progression of the underlying malignant disease; however, the associated signs, symptoms, or diagnoses should be recorded as adverse events (e.g., “jaundice” due to new or increasing liver metastases, or “tumor pain” or “bone pain” due to progressive disease);

- Medical or surgical procedures (e.g., 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 (e.g., 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;
- Pregnancy (see **Section 7.10**).

7.3 Definition of Serious Adverse Event

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death;
- Life-threatening situation (patient is at immediate risk of death);
- Inpatient hospitalization or prolongation of an existing hospitalization (excluding those for study drug administration, protocol-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events);
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- 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 a serious adverse event 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.

Clarification of Serious Adverse Events

- Death is an outcome of a serious adverse event and not a serious adverse event in itself. When death is an outcome, the event(s) resulting in death should be reported (e.g., "pulmonary embolism" with a fatal outcome). The appropriate diagnosis or term should be recorded and assigned severity grade 5;
- In instances of death due to "Disease Progression" the cause of death should be indicated as the event or condition resulting in death to the extent possible (e.g., "respiratory failure" due to progressive lung cancer). If no appropriate term with a grade 5 severity in the CTCAE can be identified, then a term should be selected from the CTCAE category "Death";

- The term “Disease Progression” should be avoided in situations in which a patient is admitted for management of conditions that are secondary to disease progression. Instead, the medical condition should be recorded (e.g., “seizure” secondary to brain metastases);
- “Occurring at any dose” does not imply that the patient is receiving study drug at the time of the event. Dosing may have been administered as treatment cycles or interrupted temporarily prior to the onset of the serious adverse event, but may still have contributed to the event;
- “Life-threatening” means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity. Grade 4 events (e.g., thrombocytopenia) are not always serious unless they have life-threatening consequences or result in hospitalization;
- Complications that occur during hospitalization are adverse events. If a complication prolongs the hospitalization, it is a serious adverse event;
- “Inpatient hospitalization” means the patient has been formally admitted to a hospital for medical reasons, for any length of time. Presentation and care within an emergency department does not necessarily constitute a serious adverse event;
- The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. If a diagnosis is unavailable at the time of initial reporting, a follow-up report should be submitted once a diagnosis is made or when the discharge summary is available.

7.4 Definition of Adverse Drug Reaction

An adverse drug reaction (ADR) is any response to a medicinal product that is noxious and/or unintended and related to any dose. The phrase “response to a medicinal product” means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

7.5 Adverse Event Reporting Period

Adverse events (as defined in section 7.2) that occur after the patient is registered/randomized and up to 30 days after the last study drug administration must be recorded as outlined in Table 7-1. Should a patient discontinue from or complete the study and commence subsequent anticancer therapy within 30 days of the last study drug administration, adverse events attributable to this subsequent therapy should **not** be recorded.

Table 7-1. Recommended Adverse Event Recording Guidelines for Phase II					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	NR	NR	Yes	Yes	Yes
Unlikely	NR	NR	Yes	Yes	Yes
Possible	Yes	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	Yes	Yes
Definitive	Yes	Yes	Yes	Yes	Yes
NR= Adverse Event will not be recorded					

Any new serious adverse event that occurs more than 30 days after last study drug administration should be reported if considered related to study drug (e.g., secondary cancer). The evaluation of an adverse event should continue until the adverse event resolves, until the start of subsequent anticancer therapy, or until the investigator or sponsor determines the patient's condition is stable.

7.6 Adverse Event Assessment and Documentation

A consistent methodology for eliciting adverse events should be adopted. Examples of non-directive questions include: "How have you felt since your last clinical visit?" or "Have you had any new or changed health problems since you were last here?" New findings on physical examination or clinically significant changes in ECGs may qualify as an adverse event. See **Section 7.8** for guidelines on reporting Clinical Laboratory Abnormalities.

Adverse events will be assessed by the investigator and recorded on the patient's chart, including the dates of onset and resolution, severity, relationship to study drug, seriousness, and the action taken with the study drug.

Correct medical terminology/concepts should be used when recording adverse event terms. Abbreviations should be avoided. A diagnosis is preferred rather than individual signs and symptoms (e.g., record pneumonia rather than fever, cough, pulmonary infiltrate).

The adjectives "severe" and "serious" are not synonymous. Serious is a regulatory definition (see **Section 7.3**), while severity describes the intensity of the adverse event. Severity should be recorded and graded according to the NCI CTCAE, v4.0 (refer to the following website for the CTC manual or the CTC document):

http://ctep.cancer.gov

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

- **Not Related:** Evidence exists that the adverse event has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered remotely or unlikely related to study drug.
- **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 rechallenge. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of adverse event reporting. This includes events that are considered possibly, probably, or definitely related to study drug.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment.

7.7 Serious Adverse Event Reporting Requirements

Serious Adverse Event Reporting for MD Anderson – IND Sponsored Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring

intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Serious Adverse Event Reporting for Astellas Pharma/OSI Pharmaceuticals

All serious adverse events related to erlotinib must be reported, by FAX (303-546-7706), to Astellas Pharma/OSI Pharmaceuticals Pharmaceuticals Drug Safety Department. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must also be reported. Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Astellas Pharma/OSI Pharmaceuticals study drug (or therapy) is suspected.

7.8 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as adverse events (or serious adverse events) if they meet the definition of an adverse event (or serious adverse event) as described in **Section 7.2** and **7.3**. In addition, laboratory abnormalities equating to DLT or any laboratory abnormalities marked as clinically significant should also be recorded as adverse events. The investigator will report the most severe grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition. All clinically significant abnormal laboratory results will be followed until they return to normal or stabilize.

7.9 Expected Adverse Events

The erlotinib Investigator's Brochure contains a complete description of the safety information for erlotinib.

An unexpected adverse event or ADR is any event for which the nature or severity is not consistent with the information contained in the Investigator's Brochure.

Based on clinical results, dermatosis or rash, diarrhea, fatigue, nausea, vomiting, stomatitis, headache, cough, dyspnea, and infection were the most frequently observed undesirable effects in cancer patients following exposure to oral erlotinib. Hematological toxicity has not been observed in patients receiving single-agent erlotinib treatment.

Diarrhea (sometimes severe) has occurred in patients receiving oral erlotinib and was mostly managed by loperamide; however, reduction in the dose of erlotinib was occasionally necessary with continuous daily dosing. There have been rare reports of renal failure and hypokalemia and some were secondary to severe dehydration due to diarrhea, nausea, vomiting, and/or anorexia. In more severe or persistent cases of diarrhea that may lead to dehydration or in patients with aggravating risk factors of renal impairment, study drug therapy should be interrupted and appropriate measures should be taken including rehydration.

There have been infrequent reports of serious ILD, including fatal events, in patients receiving erlotinib for treatment of NSCLC and other advanced solid tumors. In Study BR.21 in NSCLC patients, the incidence of ILD (0.8%) was the same in the placebo and erlotinib groups. However, one cannot completely rule out a potential causal relationship between erlotinib exposure and the rare occurrence of ILD.

In the event of acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, study drug should be interrupted pending diagnostic evaluation (see **Table 3–7**). If ILD is diagnosed, study drug should be discontinued and appropriate treatment instituted as necessary.

For further details regarding AEs considered to be possibly associated with study drug, refer to the ‘Summary of Data and Guidance for the Investigator’ section of the erlotinib Investigator’s Brochure.

7.10 Pregnancy and Breast Feeding

Erlotinib should not be used during pregnancy or while breast feeding.

8 STATISTICAL METHODS

8.1 Objectives and Design

The primary objective of this study is to assess:

- major pathologic response among patients with locally advanced oral cavity squamous cell carcinomas treated with induction cisplatin/carboplatin, docetaxel and erlotinib prior to surgery, and to compare it with the major pathologic response among patients treated with cisplatin/carboplatin, docetaxel, and placebo, in the trial population overall and in biomarker-defined subgroups.

The secondary objectives of this study are to assess:

- Safety and toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
- Recurrence-free survival
- Progression-free survival
- Response rate and disease control rate, as determined by RECIST version 1.1
- Percentage of viable tumor cells in the surgical specimen
- To correlate tissue and blood-based biomarkers with outcome and toxicity
- Quality of life, determined by the self-reported FACT-HN questionnaire

The clinical trial is divided in two stages: stage I (biomarker discovery/testing of previous findings) and stage II (biomarker-guided therapy). Fresh tissue and blood will be collected prior to initiation of induction chemotherapy for biomarker evaluation. In stage I, patients will be randomized to the control and experimental arms irrespective of their biomarker status. Upon completion of stage I, the biospecimens collected will be analyzed in search of predictive markers of benefit from erlotinib. These analyses will be informed by correlative studies of other erlotinib-based trials in HNSCC conducted at M. D. Anderson, pre-clinical data and other emerging data in the literature as regards to benefit from chemotherapy and/or EGFR inhibitors in this setting. When appropriate, techniques and cut-offs will be standardized to determine the most practical, efficient, and robust biomarkers able to discriminate responders versus non-responders to chemotherapy+erlotinib. These biomarkers (herein referred to as erlotinib associated

biomarkers [EAB]) will be CLIA certified (when appropriate) and incorporated into stage II. During stage II, patients will be adaptively randomized to the control or experimental arms according to their EAB status.

8.2 Sample Size and Trial Conduct

This study is a randomized phase 2 trial. Randomization is used to achieve patient comparability across treatments. A total of 100 evaluable patients will be randomized. Patients that are enrolled but are not randomized for any reason will be considered screen failures, and will be replaced so that the sample size achieves 100 randomized patients.

8.2.1 Randomization

Patients will be randomized to either Chemotherapy/Placebo or Chemotherapy/Erlotinib using a website housed on a secure server at MDACC and maintained by the MDACC Department of Biostatistics. Access to the website will be gained through usernames and passwords provided by the MDACC Department of Biostatistics to the research personnel at MDACC. Training on the use of the trial website to randomize patients on the study will be provided by J. Jack Lee or the designated IT personnel from the Department of Biostatistics.

This is a double-blinded randomized trial. When a patient is enrolled on the study, the patient's information as regards to stratification factors and biomarker status (when appropriate) will be entered to the database by the study personnel. After the randomization button is clicked, the patient will be assigned to a treatment arm. Information on the treatment arm will not be available to the research personnel that have direct contact with the patient (e.g., research nurses and investigators). Through the web interface, the MDACC pharmacy can enter the patient medical record number and the information on the treatment arm will be available on the screen for proper medication dispensing. All data on randomization will be stored in a secure SQL server database.

The clinical trial is divided in two stages: stage I (biomarker discovery/testing of previous findings) and stage II (biomarker-guided therapy), with 50 patients in each stage. The first 30 patients in stage I will be equally randomized between two arms, stratified by lymph node status (N0/1 vs. N2/3). Patients 31 to 50 will be adaptively randomized between the two arms based on major pathologic response and nodal status. In

stage II, upon the identification of a predictor biomarker of Chemotherapy/Erlotinib, the next 50 patients will be adaptively randomized based on response, nodal status, and the predictive biomarker (as described in **Section 8.2.2**) in order to maximize response probability based on patients' molecular profile. Adaptive randomization assigns patients into the control arm and the experimental arm with the randomization probability proportional to the treatment success using the Bayesian probit model such that more patients will be treated with the better treatment (higher overall major pathologic response rate) compared with conventional equal randomization method. The design can also maintain the pre-specified type I and type II error rates. The projected accrual rate is 3 patients per month. We expect that the study accrual will take approximately 3 years.

The primary endpoint is major pathologic response as defined in the study endpoints section which will be evaluated at the time of surgery (about 2 months from the start of the treatment). All randomized patients will be included in the primary analysis. Early drop outs prior to the time of major pathologic response evaluation will be counted as failures. We expect 33% of patients will be N0/N1, and 67% of patients will have N2/N3 status. We assume that we can identify one EAB as a predictive marker for the treatment group (cisplatin/carboplatin, and docetaxel with erlotinib) in Stage I. We also assume that the EAB positive rate is 50%. The major pathologic response rates under the null and alternative hypothesis are assumed as in **Tables 8-1a, 8-1b, and 8-1c**.

Table 8-1a: The hypothesized major pathologic response for treatment and biomarker combinations for simulation assuming 50%
biomarker positive rate.

	Null		Alternative	
Biomarker status	Control	Treatment	Control	Treatment
Negative	0.20	0.20	0.20	0.20
Positive	0.20	0.20	0.20	0.69
Overall	0.20	0.20	0.20	0.445

Table 8-1b: The hypothesized major pathologic response for treatment and biomarker combinations for simulation for N0/N1 (33% of patients)

	Null		Alternative	
Biomarker status	Control	Treatment	Control	Treatment
Negative	0.267	0.267	0.267	0.267
Positive	0.267	0.267	0.267	0.767
Overall	0.267	0.267	0.267	0.517

Table 8-1c: The hypothesized major pathologic response for treatment and biomarker combinations for simulation for N2/N3 (67% of patients)

	Null		Alternative	
Biomarker status	Control	Treatment	Control	Treatment
Negative	0.167	0.167	0.167	0.16
Positive	0.167	0.167	0.167	0.65
Overall	0.167	0.167	0.167	0.40

The Bayesian Probit Model:

A Bayesian probit model is used to predict response based on response and nodal status in the first stage, and based on response, nodal, and biomarkers in the second stage. The model is specified below:

$$Pr(y_i = 1|x_i) = \Phi(x_i^t p),$$

where y_i is the binary outcome of the i^{th} patient, Φ is the standard normal CDF, x_i is the vector of covariates of the i^{th} patient, and p is the vector of regression coefficients to be estimated. The vector of x_i includes intercept, indicator of treatment, indicator of nodal status, also may include biomarkers and their interaction terms with treatment. If treatment arm is better than the control arm, the coefficient associated with treatment will be positive; if treatment is worse than the control arm, its coefficient will be negative; if no difference then the coefficient will be zero. Effects of biomarkers and their interaction with treatment can be interpreted similarly.

A latent variable z is introduced in this Bayesian probit model, where Z_i follows a truncated normal distribution and E_i is the error term which follows an *i.i.d.* standard normal distribution specified below :

$$Z_i = x_i^t p + E_i, \text{ where } E \sim i.i.d.\ N(0,1)$$

Gibbs sampling of the probit model

Assuming a normal prior on the p, $p \sim N(b_O, B_O)$,

We have the full conditional distributions of p and z defined as:

$$B = (B_o^{-1} + X'X)^{-1}$$

$$p|z \sim N(B(B_o^{-1}b_o + X'Z), B)$$

$$Z_i|p, x_i, y_i = O \sim N(X'p, 1)[z_i < 0]$$

$$Z_i|p, x_{i,}y_i = 1 \sim N(X'p, 1)[z_i \text{ } O]$$

where X is the design matrix consist of vector of covariates $x_{i,}$.

A normal prior on p with mean 0 and standard error of 10 (a non-informative prior) will be used at the beginning of the trial. As trial goes on and data accumulates, the posterior distribution of p will be updated and inference will be made on p at the interim and at the end of the trial to make decisions.

8.2.1.1 Trial Conduct and Simulations

Within the first stage, we will equally randomize the first 30 patients into control and treatment arms stratified by nodal status to train the model before the adaptive randomization takes place. Starting from the 31st patient and up to the 50th patients, we will calculate the probability of the treatment being better than the control based on observed data irrespective to their marker status. More specifically, we will calculate the probability of treatment being better (PTB):

$$PTB = Pr(P_{trt} > P_{control} \mid Data) = Pr(x_1^t p - x_o^t p > 0 \mid Data),$$

where x_1 and x_o are covariates (treatment, nodal status) representing patients in the treatment and the control arm, respectively. We will apply a tuning parameter A (set as 0.5 by default) on *PTB* to calculate the adaptive randomization probability (*ARP*) using the following formula:

$$ARP = \frac{PTB^{;t}}{PTB^{;t} + (1 - PTB)^{;t}}$$

and patient will be randomized to the treatment arm with probability *ARP*. The randomization will be implemented in a web-based database system developed in the Department of Biostatistics to capture the patients' medical demographic variables, biomarkers, and treatment outcomes. Treatment outcome will be evaluated and entered timely to facilitate the proper implementation of the adaptive randomization.

The trial will be placed on hold for new patient accrual after the 50th patient has been randomized in stage I. At that time, we will complete biomarker analysis in tumor specimens and blood, and we will define EAB that will be used for adaptive randomization in stage II, as described in **Section 8.2.2**.

An interim analysis will be carried out after all 50 patients enrolled in the first stage have been evaluated. We will fit the probit model with only the main effect of treatment and nodal status. Three possibilities could emerge from the interim analysis:

- Interim result A (erlotinib-based therapy not beneficial): defined as $Pr(P_{trt} > P_{control} | Data) < 0.7$ for all these three sets of patients: 1) all patients, 2) marker positive patients, and 3) marker negative patients. Based on 5000 simulation trials, the probabilities of stopping for futility are 46.6% under the null and 1.4% under the alternative hypothesis (**Table 8-2**).
- Interim result B (erlotinib-based therapy beneficial, but EAB could not be defined during stage I): defined as $Pr(P_{trt} > P_{control} | Data)$ $\geq$ 0.7 in all patients, or marker positive, or marker negative, and the probability for a positive test for treatment by marker interaction is not sufficiently high, i.e. $Prob(\beta_{inter} > 0 | Data) < 0.91$.
- Interim result C (erlotinib-based therapy beneficial with corresponding EAB defined during stage I): defined as the absence of interim results A and B. Based on 5000 simulation trials, the probability of declaring erlotinib-based therapy is better than the control with the corresponding EAB identified is 60% under the alternative hypothesis and 10% under the null hypothesis.

Table 8-2: Probability of early stopping at interim analysis.

Hypothesis	Interim result A: Prob(p_trt > p_ctrl Data) < 0.7 for all three sets of patients*.	Interim result B: Prob(p_trt > p_ctrl Data) ≥ 0.7 for at least one of 3 sets of patients and Prob($\beta_{inter} > 0$!Data) < 0.91	Interim result C: Prob(p_trt > p_ctrl Data) >= 0.7 for at least one of 3 sets of patients, and Prob($\beta_{inter} > 0$!Data) ≥ 0.91
Null	0.466	0.434	0.100
Alternative	0.014	0.382	0.604

*the 3 sets of patients are 1) all patients, 2) EAB negative patients, and 3) EAB positive patients.

After the interim analysis has been completed, the trial will re-open for accrual to stage II, and treatment assignment will be performed as described below.

In interim result A, erlotinib-based induction chemotherapy has been declared not beneficial in the population overall and in the EAB negative and positive population. Therefore, all subsequent patients will be treated in an open-label fashion in Arm B with cisplatin/carboplatin and docetaxel. Patients will not receive erlotinib or placebo. Hence, the term “early stopping” refers to the stopping of the randomization in stage II. EAB may not be analyzed real time prior to treatment. A total of 50 patients will be treated in stage II. The primary analysis will be focused on describing the major pathologic response rate to induction cisplatin/carboplatin and docetaxel. Secondary analysis will focus on retrospectively identifying biomarkers predictive of major pathologic response to induction cisplatin/carboplatin and docetaxel in patients accrued to stages I and II (CAB or chemo-associated biomarker). If a CAB is identified, it could inform future clinical studies that could prospectively assess the role of this chemotherapy regimen prior to surgical resection in the CAB positive and/or CAB negative groups.

Assuming that the prevalence of the CAB for predicting chemo response is 50%, a sample size of 75 patients treated with chemo under interim result A achieves at least 74% power to detect a difference of 20% or higher in major pathologic response between the CAB positive group and the CAB negative group using Fisher’s exact test with one sided

significance level of 10% (**Table 8-3**).

Table 8-3. Power for marginally treatment effect and interaction effect at the end of stage II for interim results B and C.

	1	**2**	**3**
One-sided significance level, α	0.100	0.100	0.100
major pathologic response in	0.100	0.090	0.050
major pathologic response in	0.300	0.310	0.350
Power (%)	74	81	97
n per group	37	37	37

In interim result B, an EAB could not be defined, but erlotinib-based induction chemotherapy could be beneficial in the population overall. Therefore, randomization to arms A and B will continue, using the same algorithm applied to patients 31 to 50 in stage I (i.e., adaptive randomization based on major pathologic response). A total of 50 eligible patients will be accrued to stage II. EAB may not be analyzed prior to randomization, and EAB will not be used to influence randomization.

In interim result C, EAB has been defined and could potentially identify patients with a higher chance of major pathologic response to cisplatin/carboplatin, and docetaxel plus erlotinib. A total of 50 eligible patients will therefore be accrued to stage II. All patients will have EAB status determined prior to randomization in a CLIA certified environment. Within stage II (starting from the 51st patient), we will calculate the probability of the treatment being better than the control based on observed data and their marker status by adding two terms added to the p coefficients, the EAB status and the interaction term between treatment and EAB.

In interim results B and C, to test the overall treatment effect at end of the trial, we will fit the reduced probit model with only the intercept and the main effect of treatment and nodal status to examine whether the coefficient associated with the treatment main effect if significantly greater than 0. For each trial, we declare treatment being success

if the posterior probability of the coefficient being greater than 0 is bigger than a threshold of 0.93, i.e.

$$PSTrt = Prob(\{J_{trt} > 0 \,|Data) \geq 0.93$$

This threshold was calibrated such that our Bayesian adaptive randomization design yields a type I error rate <=10%. The overall power for the marginal effect of treatment under the alternative hypothesis is 93.2% with 10% type I error rate (**Table 8-4**).

In addition, to test the treatment by EAB interaction, a full model with main effect of treatment, nodal status, and marker, and the trt by marker interaction will be carried out to examine if the p coefficient associated with the interaction term is significantly different from zero. Formally, we declare that the EAB is a predictive marker if the posterior probability of the coefficient being greater than 0 is bigger than a threshold of delta=0.91, i.e.

$$PSI = Prob(\{J_{inter} > 0 \,|Data) \geq 0.91$$

The threshold was calibrated such that under the null (no EAB effect) the type I error rate was <= 10%. The overall power for the interaction term under the alternative hypothesis is 71.2% with 8.7% type I error rate (**Table 8-4**).

Table 8-4: Power for marginally treatment effect and interaction effect at the end of stage II for interim results B and C.

Hypotheses	Power for testing marginal treatment effect Success= $Prob(\{J_{trt} > 0 \mid Data) \geq 0.93$			Power for testing trt by EAB interaction Success= $Prob(\{J_{inter} > 0 \mid Data) \geq 0.91$		
	Interim result B	Interim result C	Overall	Interim result B	Interim result C	Overall
Null	0.0916	0.012	0.0996	0.0256	0.061	0.0866
Alternative	0.345	0.587	0.932	0.140	0.572	0.712

Details of other operating characteristics of the design based on the simulation studies were summarized in the Appendix G (**Tables A.8-5, A.8-6, and A.8-7)**.

8.2.2 Erlotinib-associated biomarkers (EAB)

After completion of stage I, accrual to the study will be placed on hold.

The biospecimens (blood and tumor tissue) collected during stage I will be analyzed in search of predictive markers of benefit from erlotinib. These analyses will be informed by correlative studies of other erlotinib-based trials in HNSCC conducted at M. D. Anderson, pre-clinical data, and other emerging data in the literature as regards to benefit from chemotherapy and/or EGFR inhibitors in this setting. Potential biomarkers to be evaluated are described in Section 6. Additional markers may be added as knowledge becomes available of their potential role as predictors of benefit from chemotherapy and/or erlotinib. When appropriate, techniques and cut-offs will be standardized to determine the most practical, efficient, and robust biomarkers able to discriminate responders versus non-responders to chemotherapy+erlotinib. These biomarkers are herein referred to as erlotinib associated biomarkers [EAB].

Before proceeding to stage II, a test for interaction will be applied to evaluate the performance of each EAB in the stage I population. EABs will be ranked according to the absolute value of the interaction term and the posterior probability of the coefficient being greater or smaller than 0. The highest ranking EABs that occur in at least 20% of

the patients accrued to stage I will be considered for selection to be incorporated into the randomization algorithm in stage II. The principal investigators, in consultation with the biostatisticians, will use their best judgment to select the final EABs to be used prospectively for randomization in stage II. In addition to the statistical properties of the model, the investigators may take into account feasibility of analyzing EABs in real time in a CLIA-certified environment, cost-effectiveness, reproducibility of the lab test and other practical aspects related to biomarker development, prior to the final EAB selection. When appropriate, two or more EABs may be combined if this improves the discriminatory abilities of pathologic responders versus non-responders to erlotinib-based therapies.

Before re-opening accrual to the trial (stage II), the selected EABs will be CLIA-certified. An amendment will be submitted to the IRB that includes, in this section of the protocol, a description of the selected EABs, and the definitions of marker positive and marker negative patients. Once the amendment is approved, the randomization algorithms will be updated and accrual to stage II will commence.

8.3 Study Endpoints

8.3.1 Safety

All patients who receive at least one treatment with any of the study drugs will be included in the safety analysis. Frequency of AEs, SAEs, discontinuation of study drug due to AEs and changes from baseline laboratory parameter values will be evaluated.

8.3.2 Efficacy

All patients randomized will be included in the efficacy analysis.

The primary efficacy endpoint is major pathologic response. The secondary efficacy endpoints are recurrence-free survival, progression-free survival, response rate and disease control rate, and percentage of viable tumor cells in the surgical specimen.

The primary analysis of efficacy is to compare major pathologic response in patients who receive erlotinib plus chemotherapy to patients who receive placebo plus chemotherapy.

8.3.2.1 Definition of major pathologic response

The following criteria will be used to guide documentation and reporting of response:

a. Complete pathological response: no residual carcinoma in the primary tumor site or lymph nodes.

b. Partial response to therapy, either i) minimal residual disease/near total effect (eg, ≤10% of tumor remaining) or ii) evidence of response to therapy but with 11%–50% of tumor remaining, or iii) >50% of tumor cellularity remains evident when compared with the previous sample, although some features of response to therapy present.

c. Minimal evidence of response to therapy.

Major pathologic response is defined as complete pathologic response or a partial pathologic response to therapy with minimal residual disease/near total effect (eg, ≤10% of tumor remaining) and no residual carcinoma in the lymph nodes.

8.3.2.2 Definition of Response by Imaging Studies

Response will be defined according to RECIST criteria as described in Appendix E.

8.3.2.3 Stable Disease Duration

The duration of stable disease will be measured from the start of treatment until the first date that progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

8.3.2.4 Progression-free and Recurrence-free Survival

Progression-free survival will be measured from the start of treatment until the first date that progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or death. Patients will be censored at the time of their last follow-up or at the time of surgery, or at the time of radiation therapy (if surgery has not been performed), whichever occurs first.

Recurrence-free survival will be measured from the date of surgery until the first date that recurrence is objectively documented or death. For patients that do not undergo surgery but receive definitive radiation therapy, recurrence-free survival will be measured from the date of completion of radiation therapy until the first date that recurrence is objectively documented or death. Patients that do not receive surgery or definitive radiation therapy will not be evaluated for recurrence-free survival.

8.3.3 Quality of Life

Quality of life data will be obtained at scheduled intervals according to **Tables 6-1** to **6-4**. Quality of life will be analyzed.

8.4 Planned Analysis

Descriptive statistics will be used to summarize the outcomes. For the primary endpoint of major pathologic response, we will use the Bayesian probit model to assess the main effect of treatment, nodal status, and biomarker, and treatment by biomarker interaction. For other binary secondary endpoints, logistic regression model will be used to assess the effect of treatment and biomarker. Cox proportional hazards models will be used to assess the effect of treatment and biomarker on time to event outcomes (recurrence free survival and progression free survival).

8.4.1 Safety

All patients who receive at least one dose of any of the study drugs will be considered evaluable for all safety analyses.

Descriptive statistics will be used to summarize safety data. Adverse events will be coded to preferred term and mapped to system organ class using a MedDRA™ dictionary, and summary tables for all adverse events will be generated. Incidence rates will be summarized for each preferred term and system organ class. Additional summary tables will be generated for the following population subsets: patients with serious adverse events, patients with related adverse events, patient deaths, and patients who discontinue due to adverse events. Depending on the doses achieved in this study, adverse events may also be summarized by dose level. Severity, investigator-attributed relationship to study drug, duration, and outcome of events will also be recorded.

8.4.1.1 Adverse Events

All adverse events will be evaluated by incidence, serious adverse events, deaths, and discontinuation due to adverse events. Severity, investigator-attributed relationship to study drug, duration, and outcome of the events will also be recorded. These adverse events will be coded to preferred term and mapped to system organ class using the MedDRA™ dictionary. The number and percent of each event will be computed and summarized by system organ class.

8.4.2 Efficacy

All randomized patients will be considered evaluable for all efficacy analyses. Efficacy will be analyzed according to the intent-to-treat principle.

8.4.3 Pharmacokinetics

Patients in Arm A and Arm B who complete 1 cycle of dosing and have erlotinib or placebo administered the day before blood collection for PK will be included in the pharmacokinetic analyses. The interactions between PKs, smoking status and efficacy will be evaluated in an exploratory fashion.

8.4.4 Quality of Life

All patients who receive at least 1 dose of study therapy will be included in the Quality of Life analyses.

9 RECORDING AND COLLECTING OF DATA

9.1 Case Report Forms

Electronic case report forms (CRFs) will be used for this study, stored under M. D. Anderson's database. In addition, DMI and CORe will be used as the electronic case report form (eCRF) for this protocol. Adverse events and protocol specific data will be entered into DMI and CORe. Concomitant medications will not be captured in case report forms in DMI. Con meds will be captured in the source document (Clinic Station).

9.2 Study Files and Patient Source Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include investigators' Study Files and original patient clinical source documents generated at the study site. The term "original" means the first recording of the data.

The investigator will ensure the Study Files are maintained, including the CRFs and query forms, protocol/amendments, IRB and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Patient clinical source documents may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, radiographs, pathology and special assessment reports, and consultant letters. The investigator must assure that all original source documents are available to support monitoring activities.

9.3 Patient Data Confidentiality

All laboratory and clinical data gathered in this protocol will be stored in a password protected database. All patient information will be handled using synonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study. Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

10 LEGAL AND ETHICAL REQUIREMENTS

10.1 Good Clinical Practice

The investigator will ensure that this study is conducted in full compliance with GCP, which includes ICH GCP guidelines, applicable GCP regulations, and with any other applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study patient.

10.2 Institutional Review Board

The investigator must submit this protocol, the informed consent form(s) to the IRB. Approval from the board/committee must be obtained before starting the study and documented in writing to the investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval. Written evidence of the approval must be made available to the sponsor. Any modifications made to the protocol after receipt of IRB approval must also be submitted to the board/committee for approval prior to implementation.

Appropriate reports on the progress of the study will be made to the IRB in accordance with applicable regulations, institutional policy, and in agreement with policies established by the sponsor.

10.3 Informed Consent

The investigator will submit the informed consent to the sponsor for approval prior to submitting to the IRB/IEC. The investigator is responsible for obtaining written, informed consent(s) from each patient interested in participating in this study prior to conducting any study-related procedures. Written informed consent should be obtained after adequate, thorough, and clear explanation of the aims, methods, objectives, potential risks and benefits of the study, as well as any use of the patient's genetic information from the study. The investigator must use the most current IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient and the person obtaining consent. The investigational site must retain the original signed consent and provide a copy to the patient. Documentation of the consent process should be documented in the subject's medical record.

Significant new safety information received by the investigator should be provided to current and future study subjects at the first available opportunity.

10.4 Study Termination

The sponsor, the investigator, and/or the regulatory authorities reserve the right to terminate the study at any time. Should termination be necessary, all parties will formulate and coordinate termination procedures. In terminating the study, the sponsor and the investigator will assure that patients' safety and rights are carefully protected.

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