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CLINICAL STUDY PROTOCOL

A RANDOMIZED, PLACEBO-CONTROLLED, PHASE 2 STUDY OF DOCETAXEL AND CISPLATIN / CARBOPLATIN WITH OR WITHOUT ERLOTINIB IN PATIENTS WITH METASTATIC OR RECURRENT SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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PROTOCOL VERSION: FINAL VERSION

PROTOCOL DATE APRIL 29, 2014

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TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Title of Study:	A Randomized, Placebo-Controlled, Phase 2 Study of Docetaxel and Cisplatin / Carboplatin with or without Erlotinib in Patients with Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck
Objectives:	The primary objective of this study is to: • Assess the efficacy of adding erlotinib to chemotherapy to improve PFS in patients with metastatic or recurrent SCCHN. The secondary objectives of this study are to: • Evaluate overall survival, response rate, disease control rate, and duration of response by treatment with or without erlotinib; • Evaluate quality of life (patient reported outcomes) by treatment with or without erlotinib; • Evaluate the safety profile of erlotinib in combination with chemotherapy; • Correlate the occurrence of erlotinib-induced rash with outcomes; • To evaluate the steady-state pharmacokinetics of erlotinib; and • To explore the prognostic and predictive value of EGFR-related biomarkers and other biomarkers, including blood and tissue proteomic and blood and tissue genomic markers, that may be associated with clinical outcomes
Study Design:	This is a randomized, placebo-controlled, phase 2 study of docetaxel and cisplatin/carboplatin with or without erlotinib in patients with metastatic or recurrent SCCHN. Patients will be randomized (1:1) to: **Arm A**: chemotherapy with concurrent erlotinib followed by maintenance erlotinib **Arm B**: chemotherapy with concurrent placebo followed by maintenance placebo All patients randomized will be followed until disease progression or death or until sufficient efficacy data have been collected to evaluate PFS and OS.
Number of Patients Planned:	120 patients (1:1 randomization)
Target Population:	Patients with metastatic or recurrent SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx, whose definitive treatment was completed ≥ 6 months prior to randomization, and for whom no chemotherapy has been administered for recurrent / metastatic disease.
Duration of Treatment:	All patients will receive up to 6 cycles of chemotherapy with concurrent erlotinib (arm A) or placebo (arm B). Patients who complete up to 6 cycles of chemotherapy with a response (CR or PR) or stable disease will continue on erlotinib (arm A) or placebo (arm B) in a maintenance phase until disease progression.
Diagnosis and Main	**Inclusion criteria**:

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Eligibility Criteria:

1. Histologically confirmed metastatic or recurrent SCCHN of the oral cavity, oropharynx, hypopharynx or larynx. Metastatic or recurrent lesions of the nasopharynx and sinus are excluded.
2. Radiologically measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan. Measurable lymph nodes are required to be ≥ 15 mm in size (short axis diameter).
3. Age ≥ 18 years.
4. ECOG PS ≤ 2.
5. Adequate bone marrow, hepatic and renal function defined by:
   a. ANC ≥ 1.5 x 10^9/L;
   b. Platelet count ≥ 100 x 10^9/L;
   c. Total bilirubin ≤ ULN (excluding Gilbert's disease);
   d. ALT (SGPT) ≤ 1.5 x ULN;
   e. Alkaline phosphatase ≤ 2.5 x ULN;
   f. Serum creatinine ≤ 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) ≤ 14 days prior to treatment initiation.
7. Written informed consent to participate in the study according to the investigational review board (IRB) or independent ethics committee (IEC).

Exclusion criteria:

1. Histology other than squamous cell carcinoma.
2. Primary sites other than oral cavity, oropharynx, hypopharynx, and larynx.
3. Prior palliative chemotherapy for metastatic or recurrent disease.
4. Prior biological therapy for metastatic or recurrent disease within 3 weeks prior to randomization.
5. Patients with known, untreated brain metastases. Patients with treated (irradiated or resected) brain metastases are eligible if treatment was completed more than 28 days prior to study entry and if clinical neurologic function is stable.
6. Pre-existing peripheral neuropathy ≥ grade 2.
7. 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.
8. Other active malignancies requiring chemotherapy treatment within 2 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical or breast cancer or superficial, resected melanoma.
9. Serious underlying medical condition which would impair the ability of the patient to receive protocol treatment, in the opinion of the treating

	physician. 10. 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. 11. Any concurrent anticancer therapy, excluding hormonal therapy for prostate or breast cancer. 12. Dementia or significantly altered mental status that would prohibit the understanding and giving of informed consent. 13. Women who are pregnant or breast-feeding and women or men not practicing effective birth control.
Study Procedures/ Frequency:	**<u>Procedures:</u>** The study will include standard procedures at baseline, during chemotherapy, following chemotherapy (maintenance phase), and at the end of treatment (approximately 30 days after the last dose of the study drug). 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 (optional) studies will be obtained, as well as a pregnancy test (when appropriate), and baseline imaging studies. Historical tissue or a new biopsy of the tumor will be obtained for biomarker analysis (optional). Eligible patients will be stratified according to recurrence-free interval (de novo metastatic disease / recurrence ≥ 6 months after definitive therapy vs. recurrence < 6 months after definitive therapy), current smoking status and prior EGFR inhibitor therapy, and will be randomized (1:1) 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, current smoking status and tobacco use, and concomitant medications use. Blood-work for hematology, biochemistry, pregnancy test (when appropriate), and blood-based biomarker studies (optional), and erlotinib PK (optional) 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) will be obtained prior to cycles 3 and 5. Patients will receive up to 6 cycles of chemotherapy with concurrent daily erlotinib (arm A) or placebo (arm B). Following chemotherapy, for patients who exhibit a complete or partial response or stable disease, maintenance erlotinib (arm A) or placebo (arm B) will be continued until disease progression. During this phase, physical exam, hematology, biochemistry studies, and pregnancy test (when appropriate) will be performed every 21 days (± 14 days). Assessment of symptoms and toxicities, and concomitant medications use will be done on an ongoing basis. Imaging studies, as well as a self-reported questionnaire for quality of life assessment (FACT-H&N), and blood-work for blood-based biomarkers (optional) and erlotinib PK (optional) will be obtained every 6 weeks (± 14 days).

	An end of treatment evaluation is planned approximately 30 days after the last dose of the study drug, and consists of a physical exam, symptoms and toxicities assessment, use of concomitant medications, and blood-work for hematology, biochemistry, pregnancy test (when appropriate) , blood-based biomarkers (optional) and erlotinib PK (optional). **Treatment Arms:** **Arm A = Chemotherapy with Concurrent Erlotinib followed by Single-Agent 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 6 cycles, plus erlotinib 150 mg PO daily continuously. A total of six cycles are planned, and a minimum of 4 cycles of chemotherapy are strongly encouraged. For patients with a complete or partial response or stable disease, erlotinib 150 mg PO daily will be continued beyond chemotherapy until disease progression. **Arm B = Chemotherapy with Concurrent Placebo followed by Single-Agent 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 6 cycles, plus placebo 150 mg PO daily continuously. A total of six cycles are planned, and a minimum of 4 cycles of chemotherapy are strongly encouraged. For patients with a complete or partial response or stable disease, placebo 150 mg PO daily will be continued beyond chemotherapy until disease progression. **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: Progression free survival Secondary endpoints: OS, RR, duration of response, quality of life, occurrence of erlotinib-induced rash, pharmacokinetics, and biomarkers.
Pharmacokinetics:	All patients who complete the pharmacokinetic sampling (optional) will be included in the pharmacokinetic analysis.
Statistical Methods:	Assuming two-sided type I error rate of 0.10, accrual rate of 4 patients per month, and additional 4 months of follow-up after the last patient is randomized, this trial will have 80% of power to detect an improvement in the median PFS from 3.0 months in Arm B to 4.9 months in arm A

	(hazard ratio=0.612), assuming 108 events (progression or death) at the time of analysis. With a total of 120 patients the accrual period will be 30 months. Kaplan-Meier methods will be used to summarize OS and PFS. In the primary analysis, differences in PFS in Arm A versus Arm B will be tested using a stratified log-rank test with a two-sided alpha of 0.10. Analyses will be stratified by recurrence-free interval (de novo metastatic disease / recurrence ≥ 6 months after definitive therapy vs. recurrence < 6 months after definitive therapy), prior EGRF inhibitor treatment, cigarette smoking status (current vs former vs never). The purpose of the statistical testing is not to draw definitive conclusions regarding the superiority of adding erlotinib to chemotherapy. A statistically significant difference (p-value ≤ 0.10) in favor of erlotinib will provide justification that a strategy of adding erlotinib to chemotherapy warrants further investigation. Hazard ratios for OS and PFS will be presented using point estimates and 95% confidence intervals. One interim analysis will be performed to allow for the early termination of the trial in light of evidence that one treatment arm is superior to the other treatment arm or there is no difference between the two treatment arms. The interim analysis will be performed when 54 out of the expected 108 events have been observed. Using O'Brien-Fleming outer test boundaries, the two-sided Z-score test cut-offs for comparing to the absolute value of the test statistics at the interim and final analyses for rejecting the null hypothesis will be 2.538 and 1.662, respectively. The inner (futility) Z-score boundaries for stopping and accepting the null hypothesis are 0.246 and 1.662. Tumor response (CR+PR), disease control (CR+PR+SD), and rash rates will be estimated by treatment arm with 95% confidence intervals. A logistic regression model will be used to test for treatment differences with terms in the model for treatment, recurrence-free interval, and smoking status. Exploratory analyses will be conducted to correlate occurrence of rash and biomarker status with outcomes to treatment.
Protocol Date:	October 2, 2012

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GLOSSARY OF ABBREVIATIONS

ADR	adverse drug reaction
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
°C	degrees Celsius
CA	Compentent Authority
C_{AVG}	average plasma concentration
CI	confidence interval
C_{max}	maximum plasma concentration
CRA	Clinical Research Associate
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CT scan	computerized tomography scan
DLT	dose-limiting toxicity
DVT	deep venous thrombosis
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for the Research and Treatment of Cancer
EOT	end-of-treatment
°F	degrees Fahrenheit
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HQoL	health-related quality of life
HPLC	high performance liquid chromatography
HR	hazard ratio
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug application
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
K	potassium
kg	kilogram
LD	lethal dose
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
Na	sodium
NCI	National Cancer Institute
NOS	not otherwise specified
ORR	objective response rate
PD	progressive disease
PE	physical examination
PFS	progression-free survival
PR	partial response
PS	performance status
QA	quality assurance
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SOC	system organ class
T_{max}	time to maximum concentration
TNM	tumor, node, metastases
TTP	time to progression
ULN	upper limit of normal
US	United States
WHO	World Health Organization

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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 carcinoma (SCCHN). Worldwide, this represents the third most prevalent cancer. Two-thirds of patients present with locally or regionally advanced disease and therapeutic efforts have focused on local control with radiation therapy (RT), chemotherapy, or combined-modality approaches and organ preservation. Sixty-five percent of these patients will relapse. Distant metastases are found in 10% of patients at diagnosis and develop in another 25% after initial treatment of the primary site. When these patients relapse, many have aggressive, platinum-resistant disease, illustrating the need for developing novel agents in this setting.

Most SCCHN 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. OSI Pharmaceuticals, Inc., Genentech, Inc., and F. Hoffmann-La Roche Ltd are co-developing erlotinib globally.

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]

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Although an overview of information pertaining to erlotinib is presented below, more comprehensive information is presented in the erlotinib Investigator's Brochure. This document should be reviewed before study initiation.

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 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 SCCHN. The overall objective response rate was 4.3%, whereas 38.3% of patients had stable disease (with a median duration of 16.1 weeks).

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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 SCCHN. 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 a single-arm, phase 2 study of the combination of cisplatin, docetaxel and erlotinib in patients with recurrent / metastatic SCCHN. 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.[8]

1.2.3 Phase 3 Experience with Erlotinib

Four randomized, placebo-controlled, phase 3 studies have been conducted with erlotinib. Three of these studies were conducted in patients with NSCLC and 1 in patients with pancreatic cancer.

Phase 3 Studies with Chemotherapy in Patients with NSCLC

Two phase 3 trials that combined daily erlotinib given concurrently with standard chemotherapy in previously untreated NSCLC patients (TALENT[9] and TRIBUTE[10]) did not meet their respective study objectives of improving survival, time to disease progression, response rate or duration of response.

Phase 3 Single-agent Study in Patients with NSCLC

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A randomized, placebo-controlled study of single-agent erlotinib at 150 mg/day in second- and third-line NSCLC (BR.21) was conducted under the sponsorship of OSI in collaboration with the NCIC CTG[3]. In this 731 patient trial, statistically significant and clinically relevant prolongation in overall survival was observed for erlotinib compared to placebo (6.7 vs 4.7 months; HR = 0.73; 95% CI: 0.60 – 0.87, *P* < 0.001), indicating that erlotinib reduced the risk of death by 27% compared with placebo. The actuarial 12-month survival rates were 31.2% and 21.5% for the erlotinib and placebo arms, respectively. Secondary endpoints of PFS and response rate were also significantly better for erlotinib.

The planned primary QoL analysis and time to deterioration of patient reported symptoms showed statistically and clinically meaningful benefit for patients randomized to erlotinib.[11]

As expected, the most common side effects were rash (75% vs 17% for placebo) and diarrhea (54% vs 18% for placebo), which were generally mild to moderate in severity and led to treatment discontinuations in only a small percentage of patients (5% for erlotinib vs 2% for placebo).[3]

Phase 3 Study in Combination with Chemotherapy in Patients with Pancreatic Cancer

A study in first-line pancreatic cancer (PA.3) was conducted under the sponsorship of OSI in collaboration with the NCIC CTG.[4] A total of 569 patients were treated with either erlotinib or placebo in combination with the approved dose-schedule of gemcitabine in pancreatic cancer (weekly × 7, 1 week off, and then weekly × 3 q 4 weeks). A statistically significant 27% improvement in overall survival (HR = 0.79) was seen in patients receiving erlotinib in combination with gemcitabine as compared to patients receiving gemcitabine plus placebo. Median and 1-year survival in the erlotinib plus gemcitabine arm were 6.4 months and 24%, respectively, as compared with 5.9 months and 17% in the gemcitabine plus placebo arm. A statistically significant improvement in PFS (HR = 0.77) was also demonstrated for the erlotinib arm.

1.3 Rationale for the Current Study

For patients with recurrent or metastatic SCCHN treated with conventional chemotherapy, response rates are in the range of 30%, median progression-free survival (PFS) is only 2 months and median overall survival (OS) is only 6 months. For example, the Liverpool Head and Neck Oncology Group randomized 200 patients to receive cisplatin alone or methotrexate alone or cisplatin plus methotrexate or cisplatin

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plus 5-fluorouracil. There was no significant difference in the response rates. A survival benefit was evident for the cisplatin alone arm compared with metotrexate alone.[12] Forastiere et al. randomized 277 patients to cisplatin plus 5-fluorouracil, carboplatin plus 5-fluorouracil or standard dosed methotrexate. The response rates were 32% for cisplatin/5-fluorouracil, 21% for carboplatin/5-fluorouracil, and 10% for methotrexate, respectively. Median survival times were similar for all three treatment groups (5.0 – 6.6 months). The duration of response was 4.2 months for cisplatin/5-fluorouracil, 5.1 months for carboplatin/5-fluorouracil and 4.1 months for methotrexate. This study supports the use of cisplatin or carboplatin-based regimens for management of HNSCC, with no clear differences in outcomes.[13] Jacobs et al. compared the cisplatin/5-fluorouracil regimen with either cisplatin alone or 5-fluorouracil alone in a randomized phase 3 trial which included 249 patients. The overall response rate to cisplatin/5-fluorouracil (32%) was superior to that of cisplatin (17%) or 5-fluorouracil (13%). However, there was neither a difference in median time to progression (1.7-2.4 months) nor survival (5.0-6.1 months) among the three groups.[14]

Combinations of a platinum salt with a taxane (docetaxel or paclitaxel), have shown the most promising results in this setting, although improved survival has not been demonstrated with any of these regimes. The paclitaxel plus cisplatin combination was directly compared to the cisplatin/5-fluorouracil regimen in the Intergroup trial E1395 conducted by the Eastern Cooperative Oncology Group. The objective response rate was 27% with the taxane-based regimen and 26% with 5-fluorouracil-based regimen. Median overall survival was 8.7 months in the cisplatin/5-fluorouracil group and 8.1 month in the cisplatin/paclitaxel group.[15] Sixty-eight patients were treated with docetaxel 65 mg/m^2 and carboplatin AUC 6 every 21 days in a SWOG phase 2 study.[16] The overall response rate was 25%. The median PFS was 3.8 months and the median overall survival 7.4 months. A phase 2 study of cisplatin and docetaxel demonstrated a response rate (RR) of 40%, median time to progression of 4 months and median OS of 9.6 months.[17]

In recent years, EGFR inhibitors have been developed for treatment of SCCHN, both in the setting of locally advanced disease (either as part of an induction chemotherapy program[18,19] or delivered concomitant with radiation therapy[20]), as well as in the setting of recurrent / metastatic disease (as single agent[1] or combined with cytotoxic chemotherapy[2]).

Cetuximab, a monoclonal antibody directed against the EGFR, has recently been approved by the FDA as first line therapy in combination with concomitant RT for the

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treatment of locally or regionally advanced SCCHN and as a single agent for second line therapy for the treatment of recurrent or metastatic SCCHN after failure of platinum-based therapy. This represented the first new drug approved in this disease in nearly 50 years. The concomitant RT study was a randomized, controlled study in 424 patients and showed improved locoregional control (24.4 vs. 14.9 mo., p=0.005) and improved survival (49.0 vs. 29.3 mo., p=0.03) for the cetuximab arm.[20]

The cetuximab monotherapy study was a single arm Phase 2 study in 103 patients who demonstrated documented progression within 30 days after 2-6 cycles of a platinum-based chemotherapy regimen. The RR was 13% with a median duration of response of 5.8 months.[1] Another single arm Phase 2 study of cetuximab and platinum chemotherapy in 96 patients with platinum-refractory recurrent or metastatic SCCHN showed a RR of 10%; median PFS was 85 days and OS was 183 days.[21] A Phase 3 ECOG study of cisplatin plus cetuximab or placebo in 117 patients with metastatic or recurrent SCCHN failed to meet the primary endpoint of improvement of PFS (4.2 vs. 2.7 mo, respectively, hazard ratio 0.78); however, patients treated with cetuximab who developed skin rash showed superior survival (p=0.013). Objective RR was significantly better for the cetuximab arm (26% vs. 10%, p=0.03).[22] A phase 3 study of platinum/5-fluorouracil +/- cetuximab involving 442 patients demonstrated a statistically significant improvement in response rate (16% versus 20%), time to treatment failure (4.8 versus 3.0 months) and OS (10.1 versus 7.4 months) for the cetuximab-containing arm.[2] Nonetheless, it is still unknown whether an EGFR inhibitor combined to a platinum/taxane based regimen will be more effective than platinum/taxane alone.

Gefitinib, a small molecule EGFR tyrosine kinase inhibitor, has also been studied in the setting of recurrent / metastatic disease. Response rates with single agent therapy have been 7.6% with 500 mg/day (n = 47) and 2.7% with 250 mg/day in a phase 3 study, with median OS of 5.6-6.0 months.[23] Nonetheless, when gefitinib was combined with cisplatin and docetaxel in a pilot phase 2 study, impressive response rates (50%) and median PFS (5.1 months) were observed.[24]

Taken together, these results demonstrate that EGFR is a valid target in the treatment of SCCHN, and that combining chemotherapy with an EGFR inhibitor in the setting of recurrent / metastatic disease might lead to improved outcomes. Indeed, the single-arm, phase 2 study of cisplatin, docetaxel and erlotinib previously reported by Kim et al.[8] met its primary endpoint: the median progression-free survival of 6 months compared favorably with historical controls from a previous phase 2 study performed at the same institution using the cisplatin and docetaxel regimen in a similar patient population

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(median PFS of 4 months).[17] Moreover the cisplatin, docetaxel and erlotinib regimen was tolerable. 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]

Hence, the present study is designed to confirm, in the setting of randomized phase 2 clinical trial, the data previously obtained by Kim et al.[8] The results of the present study might justify, in the future, further investigation of the cisplatin, carboplatin, docetaxel, erlotinib regimen in the scenario of a phase 3 study.

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2 STUDY OBJECTIVES

The primary objective of this study is to:

- Assess the efficacy of adding erlotinib to chemotherapy to improve PFS in patients with metastatic or recurrent SCCHN.

The secondary objectives of this study are to:

- Evaluate overall survival, response rate, disease control rate, and duration of response by treatment with or without erlotinib;
- Evaluate quality of life (patient reported outcomes) by treatment with or without erlotinib;
- Evaluate the safety profile of erlotinib in combination with chemotherapy;
- Correlate the occurrence of erlotinib-induced rash with outcomes;
- To evaluate the steady-state pharmacokinetics of erlotinib; and
- To explore the prognostic and predictive value of EGFR-related biomarkers and other biomarkers, including blood and tissue proteomic and blood and tissue genomic markers, that may be associated with clinical outcomes

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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 metastatic or recurrent SCCHN. Patients will be randomized (1:1) to:

Arm A — chemotherapy with concurrent erlotinib followed by maintenance erlotinib;

Arm B — chemotherapy with concurrent placebo followed by maintenance placebo.

All patients randomized will be followed until death or until sufficient efficacy data have been collected to evaluate PFS and OS. A schematic diagram of the study design is shown in **Figure 3–1**.

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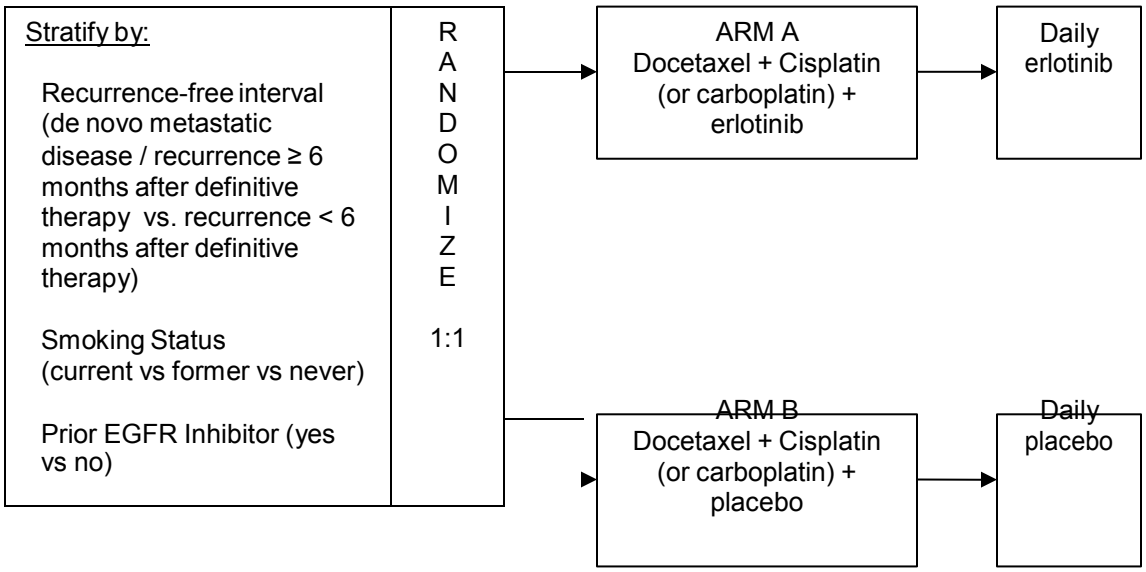
Figure 3–1: Study Schematic



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

- Recurrence-free interval (de novo metastatic disease / recurrence ≥ 6 months after definitive therapy vs. recurrence < 6 months after definitive therapy);
- Cigarette smoking status (current vs former vs never).

  Definitions of cigarette smoking status:

  - **Current cigarette smoker:** has smoked > 100 cigarettes in entire lifetime and is either currently smoking or quit smoking < 1 week prior to randomization
  - **Former cigarette smoker:** has smoked > 100 cigarettes in entire lifetime and quit smoking ≥ 1 week prior to randomization
  - **Never smoker:** has smoked ≤ 100 cigarettes in entire lifetime and stopped or never smoked cigarettes
- Prior EGFR Inhibitor Therapy (yes vs no)

3.1 Treatment Plan and Regimen

3.1.1 Treatment Plan

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

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Arm A: Chemotherapy (up to 6 cycles) with erlotinib followed by daily erlotinib; or

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Arm B: Chemotherapy (up to 6 cycles) with placebo followed by daily placebo

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

In both arms, six cycles of chemotherapy are planned, and at least 4 cycles of chemotherapy are strongly recommended. 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.

In Arm A, erlotinib will be administered daily throughout the study. In Arm B, placebo will be administered daily throughout the study. After discontinuation of chemotherapy, patients with a response (CR or PR) or stable disease will continue to receive daily erlotinib (in Arm A) or daily placebo (in Arm B), at the most recent dose, until objective disease progression or death or intolerable toxicity. A schedule of study drug administration is shown in **Table 3–1**. Treatment must 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:

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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) =

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6 x 150 mL/min = 900 mg **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	Continuously [b]
	Erlotinib	150 mg/day	PO	
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	Continuously [b]
	Placebo	150 mg/day	PO	

[a] For a maximum of 6 cycles.

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[b] If the patient completes 6 cycles of chemotherapy with a response (CR or PR) or stable disease daily erlotinib (in Arm A) or daily placebo (in Arm B), at the most recent dose, will be continued until objective disease progression or death or intolerable toxicity.

If the patient completes < 6 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 objective disease progression or death or intolerable toxicity.

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. Delaying or discontinuing one chemotherapy agent (docetaxel or cisplatin/carboplatin) will result in delaying or discontinuing of the other chemotherapy agent (cisplatin/carboplatin or docetaxel). Docetaxel or cisplatin/carboplatin 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.

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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 ≥ 7 days
- Grade 3 or 4 febrile neutropenia

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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**.

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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.

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.

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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 ≤ 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],

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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.

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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 ≥ 1.5 x 10^9/L and a platelet count ≥ 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 ≤ 3 weeks. If the patient is unable to be treated after a 3-week delay, the patient will be discontinued from chemotherapy. Patients who require docetaxel discontinuation (for any reason) will also discontinue cisplatin / carbopatin treatment. Patients who require cisplatin / carboplatin discontinuation (for any reason) will also discontinue docetaxel treatment. Patients who have discontinued chemotherapy will be allowed to continue on daily, single-agent erlotinib or placebo as described in **Section 3.1.1**.

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

DAY 1 COUNTS AND MAJOR ORGAN TOXICITY GRADING			
Neutrophils (× 10^9/L)		**Platelets (× 10^9/L)**	**Timing**
≥ 1.5	**AND**	≥ 100	Treat on time
< 1.5	**OR**	< 100	Delay until recovery*
* If patient does not recover in ≤ 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.

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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.

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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.

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3.1.3.2 Erlotinib or Placebo Dose Interruptions

Patients who have a continuous interruption of erlotinib or placebo dosing for ≤ 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.

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4 PATIENT POPULATION

Patients with histologically confirmed metastatic or recurrent SCCHN of the oral cavity, oropharynx, hypopharynx or larynx who have an ECOG performance status of 0-2, measurable disease and no prior chemotherapy for their metastatic or recurrent disease will be enrolled.

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. Histologically confirmed metastatic or recurrent SCCHN of the oral cavity, oropharynx, hypopharynx or larynx. Metastatic or recurrent lesions of the nasopharynx and sinus are excluded.
2. Radiologically measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan. Measurable lymph nodes are required to be ≥ 15 mm in size (short axis diameter).
3. Age ≥ 18 years.
4. ECOG PS ≤ 2 (Appendix B)
5. Adequate bone marrow, hepatic and renal function defined by:
   a. ANC ≥ 1.5 x 10^9/L;
   b. Platelet count ≥ 100 x 10^9/L;
   c. Total bilirubin ≤ ULN (excluding Gilbert's disease);
   d. ALT (SGPT) ≤ 1.5 x ULN;
   e. Alkaline phosphatase ≤ 2.5 x ULN;
   f. Serum creatinine ≤ 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) ≤ 14 days prior to treatment initiation.
7. Written informed consent to participate in the study according to the investigational review board (IRB) or independent ethics committee (IEC).

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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, oropharynx, hypopharynx, and larynx.
3. Prior palliative chemotherapy for metastatic or recurrent disease.
4. Prior biological therapy for metastatic or recurrent disease within 3 weeks prior to randomization.
5. Patients with known, untreated brain metastases. Patients with treated (irradiated or resected) brain metastases are eligible if treatment was completed more than 28 days prior to study entry and if clinical neurologic function is stable.
6. Pre-existing peripheral neuropathy ≥ grade 2.
7. 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.
8. Other active malignancies requiring chemotherapy treatment within 2 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical or breast cancer or superficial, resected melanoma.
9. Serious underlying medical condition which would impair the ability of the patient to receive protocol treatment, in the opinion of the treating physician.
10. 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.
11. Any concurrent anticancer therapy, excluding hormonal therapy for prostate or breast cancer.
12. Dementia or significantly altered mental status that would prohibit the understanding and giving of informed consent.
13. Women who are pregnant or breast-feeding and women or men not practicing effective birth control.

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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

OSI 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.

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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

OSI requires that a drug accountability log for erlotinib (Arm A) or placebo (Arm B) 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, the unused, used and expired study drug will be destroyed at MDACC per Institutional SOPs and OSI will be provided with documentation when this has occurred.

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5.5 Treatment Compliance

Compliance of erlotinib (Arm A) or placebo (Arm B) will be assessed by counting tablets at the scheduled patient 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 chart.

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.[25] Patients who fail to respond to these measures

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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

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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 ≥ 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 Radiotherapy and Surgery

No radiotherapy is allowed during treatment. For the rare patient who experiences response to the investigational treatment and is able to undergo salvage and/or consolidation surgery and/or radiotherapy, treatment with erlotinib (Arm A) or placebo (Arm B) single agent may be resumed after surgery and/or radiotherapy (even if treatment interruption has been longer than 21 days) and continued until disease progression, after approval by the principal investigator of the trial.

5.6.2.3 Palliative Concomitant Medication

Patients may receive palliative concomitant medication while on study.

5.6.2.4 Other Investigational Drug Therapies

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

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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 C).

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.

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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

Unblinding of single cases by the investigator will only be performed if relevant for the safety of the participant. In emergency situations, the investigator would contact the study statistician and pharmacy to obtain immediate blinding information for the participant. The information will be forwarded to the investigator to enable the participant to be treated. In non-emergency situations, the same procedures would

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apply, however the study statistician will discuss and evaluate the request, then, would be responsible for making the decision of whether or not to unblind.

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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 presented in **Appendix A** and detailed in the text that follows.

6.1 Patient Enrollment and Treatment Assignment

Before recruitment of patients into the study, written IRB/IEC 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 must start treatment within 14 days of randomization.

Investigators will be notified when the target enrollment in each treatment arm has been reached.

6.2 Baseline Assessments

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

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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	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	• Chest X-ray **and** • CT or MRI scans of **all** disease sites (excluding bones) • Additional imaging studies as clinically indicated	Within 30 days prior to treatment initiation
Tumor Tissue Collection for Biomarkers (optional)	• Either historical or new biopsy of primary lesion and/or lymph node and/or metastatic site for biomarker analysis	Prior to treatment initiation
Blood-based biomarkers (optional)	• Blood sample	Within 30 days prior to treatment initiation

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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**.

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

Investigations			Timing
Physical Exam Including:	• BSA • Vital signs		Within 7 days prior to cycles 2-6
Current Smoking Status and Tobacco Use[1]	• Assessment of patient's current smoking status and tobacco use		Within 7 days prior to cycles 2-6
Hematology	• CBC with hemoglobin, platelets, and WBC with differential		Within 7 days prior to cycles 2-6
Biochemistry[1]	• Albumin • Alkaline phosphatase • Total bilirubin • BUN • Creatinine	• Glucose • LDH • Potassium • SGOT (AST) • SGPT (ALT) • Sodium • Magnesium	Within 7 days prior to cycles 2-6
Pregnancy Test	• Urine or serum (for women of childbearing potential only)		If/when clinically indicated
Radiology [1]	• Chest X-ray **and** • CT or MRI scans of **all** disease sites (excluding bones). • Additional imaging studies as clinically indicated		Within 7 days prior to cycles 3 and 5
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		Within 7 days prior to cycles 3 and 5
Blood-based biomarkers[1] (optional)	• Blood sample		Within 7 days prior to cycles 2-6
Erlotinib PK[1] (optional)	• Blood sample		Within 7 days prior to cycles 2-6
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.			

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6.3.2 Assessments Following Chemotherapy

After completing chemotherapy, patients will be evaluated every 21 days (± 14 days) according to the assessments outlined in Table 6-3 until objective disease progression or death.

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Table 6–3: Assessments Following Chemotherapy

Investigations		Timing
Physical Exam Including:	• Vital Signs	Every 21 days (± 14 days)
Current Smoking Status and Tobacco use	• Assessment of patient's current smoking status and tobacco use	Every 21 days (± 14 days)
Hematology	• CBC with hemoglobin, platelets, and WBC with differential	Every 21 days (± 14 days)
Biochemistry	• Total bilirubin, creatinine and SGPT (ALT), sodium, magnesium	Every 21 days (± 14 days)
Blood-based biomarkers (optional)	• Blood sample	Every 6 weeks (± 14 days) until disease progression or death
Erlotinib PK (optional)	• Blood sample	Every 6 weeks (± 14 days) until disease progression or death
Pregnancy Test	• Urine or serum (for women of childbearing potential only)	If/when clinically indicated
Radiology	• Chest X-ray **and** • CT or MRI scans of **all** disease sites (excluding bones). • Additional imaging studies as clinically indicated	Every 6 weeks (± 14 days) until disease progression or death
Symptoms & Toxicities	• Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v4.0	On an ongoing basis until the final study visit
Concomitant Medications	• Documentation of concomitant medications	On an ongoing basis until the final study visit
Quality of Life	• FACT-H&N	Every 6 weeks (± 14 days) until disease progression or death
Erlotinib Treatment Compliance	• Count tablets and record findings	At each clinic visit

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6.3.3 End of Treatment Assessments

For all patients, the End of Treatment Visit will occur approximately 30 days after the last dose of study drug (i.e., 30 days after the last dose of erlotinib maintenance treatment). At this visit, patients will be evaluated according to the assessments outlined in **Table 6–4**.

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Table 6–4: End of Treatment Assessments

Investigations		Timing
Physical Exam Including:	• Vital Signs	Approximately 30 days after the last dose of study drug
Hematology	• CBC with hemoglobin, platelets, and WBC with differential	Approximately 30 days after the last dose of study drug
Biochemistry	• Total bilirubin, creatinine and SGPT (ALT)	Approximately 30 days after the last dose of study drug
Blood-based biomarkers (optional)	• Blood sample	Approximately 30 days after the last dose of study drug
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Erlotinib PK (optional)	• Blood sample	Approximately 30 days after the last dose of study drug
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	Approximately 30 days after the last dose of study drug
Concomitant Medications	• Documentation of concomitant medications	Approximately 30 days after the last dose of study drug

6.4 Descriptions of Study Assessments

6.4.1 Smoking History

The smoking history of all patients will be collected within 14 days prior to randomization. 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 ≥ 1 week before randomization

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- **Never smoker:** has smoked ≤ 100 cigarettes in entire lifetime and stopped or never smoked cigarettes

For all patients, smoking status will be re-evaluated at each clinic visit**.**

Tobacco use other than cigarette smoking will also be assessed at baseline and according to **Tables 6-1** to **6-3**.

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 **6-3**.

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. All adverse events that occur from the time of study drug administration until the completion of the study will be recorded on the patient's chart as an adverse event, regardless of the potential relationship to the study drug. The date of onset, severity, and investigator's opinion of potential relationship of the event to protocol therapy will be recorded.

6.4.5 Radiology Assessments

Chest X-rays and CT or MRI scans of all disease sites (excluding bone) will be obtained according to **Tables 6-1** to **6-3**. 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[26] (see Appendix D), 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 (i.e., scans performed immediately following bolus contrast administration should be made with a standard volume of contrast, the identical contrast agent).

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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 **6-3**.

6.4.7 Tumor Tissue Samples

Optional baseline tumor tissue samples from either the primary lesion and/or lymph node and/or metastatic site (either historical or new biopsy) will be collected for exploratory analyses of biomarkers. For newly collected tissues, samples will be obtained by an outpatient core biopsy, or a punch-biopsy performed under local anesthesia 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 may 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.

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), micro-RNA and messenger-RNA expression levels (using high-throughput microarray chips), high-throughput genomic 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

Optional blood will be collected, at scheduled intervals according to **Tables 6-1** to **6-3,** using three (3) EDTA (10 mL) 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

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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. For serum samples, blood will be centrifuged in a standard clinical centrifuge at 2500 RPM at 4 ^{o}C for 10 minutes. Aliquots of 2.0-2.5 mL should then be transferred into cryovials, labeled with the protocol number and the patient's unique study identification number. Cryovials will be stored at -80 ^{o}C.

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 (Bio-Plex 27-Plex & 23-Plex Kits [Bio-Rad, Hercules, CA] and Human CVD Biomarker Panel 1 [Linco Research, Inc., St, Charles, MO]), VEGF, solubleVEGFR-1, soluble VEGFR-2, osteopontin, free and total IGF-1 and IGF-2, IGFBP-3, insulin, peptide C, free fatty acids, triglycerides, fructosamine, high-throughput proteomic analysis, high-throughput genomic analysis 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 samples may be analyzed in the future for biomarkers not described in this protocol.

6.4.10 End of Treatment Assessments

If a patient has not progressed or died by the End of Treatment visit (30 days after the last dose of study drug), quality of life and radiology assessments may continue to be collected. All new serious adverse events occurring more than 30 days after last study drug administration (i.e., after the End of Treatment visit) and considered at least possibly drug-related must be reported to OSI. See **Section 7.7** for serious adverse event reporting requirements.

6.4.11 Long-Term Follow-Up

After the End of Treatment visit, information may be collected on post-study additional therapies, disease response / progression, and long-term survival, as well as any new or ongoing drug-related adverse events. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during

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clinic visits after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews.

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 6.4.11**).

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6.6 Criteria for Study Discontinuation

Study medication should be discontinued in the following instances:

- Relapse or disease progression (patients with evidence of clinical or symptomatic benefit despite radiological progression may continue treatment with erlotinib upon agreement between OSI and the investigator);
- 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 up to 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).

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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** 6. 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).

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 on the appropriate CRF page.

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);

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- 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 Serious Adverse Event Reporting Requirements

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

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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dycrasias or convulsions that do not result in hospitalization, or 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).

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- **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.

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

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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

Any adverse event (i.e., a new event or an exacerbation of a pre-existing condition) that occurs after the patient is registered/randomized and up to 30 days after the last study drug administration must be recorded as an adverse event on the appropriate page(s) of the CRF. 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. 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.

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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.

All 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.

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7.7 Serious Adverse Event Reporting Requirements

Serious Adverse Event Reporting to OSI Pharmaceuticals

All serious adverse events related to erlotinib must be reported, by FAX (303-546-7706), to OSI 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 OSI 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

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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. Men and premenopausal women of child-bearing potential must use one of the following forms of birth control Birth Control Specifications: You should use birth control, such as barrier methods, condom or diaphragm with spermicide, or abstinence, while participating in the study and for 30 days following the last dose of the study drug.
Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant will result in your removal from this study.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.Pregnancy and breast feeding are exclusion criteria. If a female patient or

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partner of a male patient becomes pregnant while receiving study drug or within 120 days after the last dose of study drug, a Pregnancy Form must be completed and submitted to the sponsor in a timely manner. The pregnancy must be followed during the entire course, with perinatal and neonatal outcomes recorded even if completely normal and without an adverse event.

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8 STATISTICAL METHODS

8.1 Objectives and Design

8.2 Sample Size

A sample size of 120 patients (randomized 1:1 to Arm A and Arm B) will be needed to detect a 1.9 month improvement in the median PFS (from 3.0 to 4.9 months) in the erlotinib-containing arm over the placebo arm. The corresponding hazard ratio between arm A and arm B is 0.612 based on the assumption that the time to event follows an exponential distribution. Assuming two-sided type I error rate of 0.10, accrual rate of 4 patients per month, and additional 4 months of follow-up after the last patient is randomized, a trial with 60 patients each arm will have 80% of power to detect a 1.9 month improvement in the median PFS, assuming 108 events (progression or death) at the time of analysis. With a total of 120 patients the accrual period will be 30 months.

8.2.1 Randomization

An adaptive randomization method by Pocock and Simon[27] will be used with a minimization probability parameter of 0.90. The randomization process will be controlled to ensure a balanced stratification by treatment arm for the following factors:

- Cigarette smoking status (current vs former vs never);
- Recurrence-free interval (de novo metastatic disease / recurrence ≥ 6 months after definitive therapy vs. recurrence < 6 months after definitive therapy); and
- Prior EGFR inhibitors (yes vs no)

Patients will be randomized to either Chemotherapy/Placebo or Chemotherapy/Erlotinib using the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct) which is 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 pharmacy personnel at MDACC.

Training on the use of the Clinical Trial Conduct website to randomize patients on the study will be provided by Lei Feng from the Department of Biostatistics for the pharmacy personnel at MDACC. This is a double-blinded trial with stratified randomization. When a patient is enrolled on the study, the research nurse of the study will email the MDACC pharmacy with patient's information on medical record number and stratification factors. Through the web interface, the MDACC pharmacy can enter the patient medical record number and the information on stratification factors. After the randomization button is clicked, the result of the randomization will be displayed on the screen for the pharmacy to view. For all other clinical personnel on the study, the information on treatment will be blinded. All data on randomization will be stored in a secure SQL server database.

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8.3 Study Endpoints

8.3.1 Safety

All patients who receive at least 1 treatment study 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 PFS. The secondary efficacy endpoints are OS, RR, duration of response, quality of life, occurrence of erlotinib-induced rash, PK, and biomarkers.

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

8.3.2.1 Definition of Response

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

8.3.2.2 Response Duration

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

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 Overall 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.

Overall survival will be measured from the start of treatment until death.

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8.3.3 Quality of Life

Quality of life data will be obtained at scheduled intervals according to **Tables 7-1** to **7-3**. Quality of life will be analyzed.

8.4 Interim Analysis

One interim analysis will be performed to allow for the early termination of the trial in light of evidence that one treatment arm is superior to the other treatment arm or there is no difference between the two treatment arms. In order to provide an overall significance level of 0.10 for the study, the interim analysis will use a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule.[28] The interim analysis will be performed when 54 out of the expected 108 events have been observed. Using O'Brien-Fleming outer test boundaries, the two-sided Z-score test cut-offs for comparing to the absolute value of the test statistics at the interim and final analyses for rejecting the null hypothesis will be 2.538 and 1.662, respectively. The inner (futility) Z-score boundaries for stopping and accepting the null hypothesis are 0.246 and 1.662..

8.5 Planned Analysis

Data will be summarized for arms A and B. Kaplan-Meier methods will be used to summarize OS and PFS. Analyses will be stratified by recurrence-free interval (de novo metastatic disease / recurrence ≥ 6 months after definitive therapy vs. recurrence < 6 months after definitive therapy), prior EGFR inhibitor treatment, and cigarette smoking status (current vs former vs never). Hazard ratios for OS and PFS will be presented using point estimates and 95% confidence intervals.

Tumor response (CR+PR) and disease control (CR+PR+SD) will be estimated by treatment arm with 95% confidence intervals. A logistic regression model will be used to test for treatment differences with terms in the model for treatment, recurrence-free interval, and smoking status.

A two-sided alpha (i.e., significance level) of 0.10 will be used to compare treatment arms, following the approach proposed by Korn et al.[29] and Simon et al.[30] The purpose of the statistical testing is not to draw definitive conclusions regarding the superiority of adding erlotinib to chemotherapy. A statistically significant difference (p-value ≤ 0.10) in favor of erlotinib will provide justification that a strategy of adding erlotinib to chemotherapy warrants further investigation

Exploratory analyses will be conducted to correlate occurrence of rash and biomarker status with outcomes to treatment.

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8.5.1 Safety

All patients who receive at least 1 dose of erlotinib 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.

8.5.1.1 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.

8.5.2 Efficacy

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

8.5.3 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.

8.5.4 Quality of Life

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

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9 STUDY CONDUCT

9.1 Adherence to the Protocol

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

Changes to the protocol may be made only when a written protocol amendment provided by the sponsor has been signed by the investigator and approved by the IRB and applicable regulatory agencies in accordance with local requirements.

9.2 Recording and Collecting of Data

9.2.1 Case Report Forms

Electronic case report forms (CRFs) will be used for this study, stored under M. D. Anderson's Protocol Data Management Systems (PDMS) database.

9.2.2 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.

9.2.3 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

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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.

9.3 Legal and Ethical Requirements

9.3.1 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.

9.3.2 Institutional Review Board/Independent Ethics Committee Approval

The investigator must submit this protocol, the informed consent form(s) to the IRB/IEC. 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/IEC 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/IEC in accordance with applicable regulations, institutional policy, and in agreement with policies established by the sponsor.

9.3.3 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/IEC-

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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.

9.3.4 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.

9.3.5 Regulatory Approval

The sponsor will determine the appropriate local, national, and/or regional regulatory approval(s) that need to be obtained in order to conduct this study.

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