

**A Phase II Study of Erlotinib (Tarceva®) in Combination with Bexarotene (Targretin®) in
Chemorefractory Patients with Advanced Non-small Cell Lung Cancer**

Sponsor Version #9

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Our plan is to develop individualized targeted therapy, with or without chemotherapy, based on the identification and validation of specific molecular pathways of NSCLC. To address these new targeted therapeutic approaches, we propose to develop an integrated, translational lung cancer research program entitled, "BATTLE: Biomarker-integrated Approaches of Targeted Therapy of Lung Cancer Elimination," and provide a strong rationale-based targeted treatment strategy. The proposed program capitalizes on our rich understanding of lung cancer biology, our capability to develop and analyze biomarkers, our experience with clinical trial implementation, enrolling large numbers of patients with advanced non-small cell lung cancer (NSCLC), and the availability of several promising agents, which target different pathways critical for patient survival of NSCLC.

1.3 Specific Aims

The following are the specific aims of the BATTLE clinical trial program. This protocol is one of the phase II trials that is part of the BATTLE program.

Specific Aim 1: To establish a clinical trial program using biomarkers to select targeted therapy for chemorefractory, advanced NSCLC patients. The proposed clinical trials will integrate biomarker assessment and offer the most promising targeted agents into a clinical trial designed to best benefit patients from each treatment. According to the statistical assessment of their molecular profiles performed in Biomarker Core and Biostatistics Core, patients will be initially stratified into one of four clinical trials.

- Erlotinib trial for patients with somatic EGFR mutation or overrepresentation
- ZD6474 trial for patients with increased VEGF and / or VEGFR
- Bexarotene + Erlotinib trial for patients with expressed RXRs and/or increased Cyclin D1
- Bay43-9006 trial for patients with mutated K-ras or B-raf

Specific Aim 2: To investigate molecular mechanisms of response or resistance to the targeted agents on their putative targeted signaling pathways focused in the study. We will examine effects of these agents on their putative targets and downstream effectors using *in vitro* and *in vivo* models, in order to determine whether these biomarker modulation effects are correlated with patient responses. Specifically, we will investigate:

- To validate molecular mechanisms of response or resistance to erlotinib for patients with previously treated NSCLC
- To determine the role of insulin-like Growth Factor 1 Receptor (IGF-1R) Signaling Pathways in resistance to Erlotinib in NSCLC Cells
- To identify VEGF pathway biomarkers for prediction of clinical outcomes of anti-angiogenesis inhibitors
- To investigate molecular mechanisms of effects of the combination of bexarotene and erlotinib on NSCLC cells

Specific Aim 3: To identify novel biomarkers for prediction of clinical endpoints to the targeted agents used in the study and potential new therapeutic targets. The clinical trial proposed in Specific Aim 1 will provide valuable patient specimens and clinical outcome data. Such samples and data will allow us to conduct global genomic and proteomic analyses in order to maximize the possibility of

1 INTRODUCTION

1.1 Non-small cell lung cancer

Lung cancer is the leading cause of death worldwide and in the US. An estimated 175,000 new cases of lung cancer were diagnosed in the US in the year 2005 leading to approximately 165,000 deaths in the United States alone (Jemal 2005). Non-small cell lung cancer (NSCLC) accounts for almost 80% of newly diagnosed cases. Lung cancer deaths in the US surpass those resulting from breast, prostate, and colon cancers, and its incidence continues to rise.

Only 16% of these patients in whom lung cancer develops live 5 years or more after the diagnosis is made. Despite substantial effort in developing methods for early diagnosis and treatment of lung cancer in the last two decades, more than 80% of patients when diagnosed have either locally advanced unresectable or metastatic disease and their chance to be cured by current oncology practice is low.

At presentation, the median survival for patients with advanced disease defined as inoperable Stage 3 or 4 non-small-cell lung cancer (NSCLC) is 8 to 10 months, with a one-year survival of 35 to 45% (Reck 2004). In NSCLC as with other cancers, median survival following a second relapse is even shorter and decreases progressively with each subsequent treatment. In those patients who have a good enough performance score to be able to tolerate chemotherapy and receive docetaxel as a second chemotherapy, subsequent median survival is 7.5 months for docetaxel-treated patients and 4.6 months for patients treated with best supportive care (Shepherd 2000). For those patients who have received two prior chemotherapy regimens, the subsequent median survival is likely to be even shorter and the ability to tolerate intensive or additional chemotherapy further compromised due to both cumulative therapy-related toxicities and prolonged periods of time with advanced disease.

1.2 Molecularly Targeted Therapy

Advances in molecular biology, particularly the completion of the Human Genome Project, have led to substantial knowledge about the molecular basis of lung cancer, which provides a unique opportunity to develop novel strategies to target key pathways crucial for lung cancer development. This has led to emerging targeted therapy to attack lung cancer. However, to answer the question of how to develop "smarter" clinical trials using informative molecular markers, we must first identify these biomarkers and then target these markers with specific molecular inhibitors. Several large, randomized trials using targeted agents either alone or combined with chemotherapy, failed to demonstrate the contribution of the targeted agent in the treatment of lung cancer (Herbst 2004, 2004, Gatzmeier 2004). Even when positive, such as the recent bevacizumab trial with chemotherapy, the magnitude of benefit has been small, suggesting the need for optimization of patient selection and more active agents (Sandler 2005). The major reasons for suboptimal results are either the agent used for treatment does not effectively hit the target, or the agent does hit the target, but activates other pathways, which promotes survival and leads to further progression. Thus, it is unlikely that the empirical use of targeted agents in the treatment of lung cancer is going to make a more significant impact without a greater focus on prognostic markers and scientific data. The recent discovery that somatic mutations in the EGFR kinase domain correlate and predict responses to the EGFR kinase inhibitor, Gefitinib or Erlotinib, underscores the importance of tailored individualized therapy based on the tumors' underlying molecular biological profiles (Lynch 2004, Kobayashi 2005).

identifying new biomarkers for predicting clinical outcomes, mechanisms of response/resistance, and potential therapeutic targets.

Specific Aim 4: To explore new preclinical combinations and their mechanism of action by targeting mTOR signaling and develop Phase I trials to test these combinations.

1.4 Epidermal Growth Factor Receptor (EGFR) and Retinoid Signaling Pathway

EGFR Signaling

The epidermal growth factor receptor (EGFR) is a 170kD transmembrane glycosylated phosphoprotein with tyrosine kinase activity and is a member of the Erb-B receptor tyrosine kinase family that includes Erb B-2(Her-2), Erb B-3, and Erb B-4 (Mendelsohn 2001).¹ It consists of an extracellular ligand-binding domain, a transmembrane region that anchors the receptor to the plasma membrane, and a cytoplasmic region containing a tyrosine kinase domain. The principal natural ligands of EGFR in human tissues are epidermal growth factor (EGF) and transforming growth factor α (TGF- α), both of which activate the receptor by binding to the extracellular domain and inducing the formation of receptor homodimers or heterodimers, followed by internalization of the receptor/ligand complex and auto-phosphorylation. Activation of the receptor initiates multiple potential intracellular signal transduction cascades. Other ligands for EGFR include amphiregulin, heparin-binding EGF (HB-EGF), and beta-cellulin. It is now accepted that the EGFR signal transduction network plays an important role in multiple tumorigenic processes, including cell cycle progression, angiogenesis, and metastasis, as well as protection from apoptosis (Huang 2000, Mendelsohn 2003). EGFR is known to participate in cell proliferation (ras/raf/MAP kinase pathway), inhibition of apoptosis (PI3 kinase/Akt pathway), tumor cell motility and metastasis.

Studies in head and neck squamous cell carcinoma cell lines and preclinical animal models have shown that inhibition of EGFR will arrest cell proliferation and tumor growth. Due to its ability to promote tumorigenesis, EGFR is a promising target for biological therapy. Several places of EGFR action are promising targets of inhibition; these include the ligandbinding site, kinase activation, protein production and downstream signaling pathways (Huang 2001).

There is now considerable evidence of expression and over-expression of EGFR in an extensive range of human cancers, e.g., non-small cell lung cancer (NSCLC) as well as prostate, colorectal, head and neck, bladder, breast, and gastric cancers (Carpenter 1990, Grandis 1998). Importantly, over-expression of EGFR has been correlated with poor prognosis features in many cases (Wickstrand 1998).

Retinoid Signaling Pathway

The retinoids, natural and synthetic derivatives of vitamin A, exert antiproliferative, differentiation-inducing as well as pro-apoptotic effects. Retinoids play a critical role in the regulation of cell division, growth, differentiation, and proliferation (Freemantle 2003, Dragnev 2003).

They are able to invert cancerous progression in the airway by complex mechanisms. These mechanisms essentially depend on the retinoids' capacity to regulate gene expression through nuclear transduction signal modulation mediated by nuclear retinoid receptors. These receptors act as ligand-activated transcription factors. It has been demonstrated that expression of retinoic acid

receptor (RAR- β), one of these receptors, is inhibited in early stages of head and neck carcinogenesis (pre-malignant lesions of the oral cavity and tumors adjacent to dysplastic tissues) and in lung carcinogenesis. Expression of this receptor could be restored by administration of 13-*cis* retinoic acid (13-cRA). These results have been confirmed by *in vivo* studies (Xu 1994, Lotan 1995).

Retinoid X receptor (RXR, rexinoids) and classical retinoid receptor agonists activate distinct nuclear receptors, but can engage related pathways. A rexinoid can bypass RAR-beta repression, which is frequent in NSCLC and likely contributes to resistance to classical retinoids that activate RARs.

1.5 Erlotinib (Tarceva™)

Erlotinib (Tarceva™) is an active oral quinazoline that selectively inhibits EGFR tyrosine kinase, prevents autophosphorylation of EGFR, and arrests cell cycle growth in the G₀/G₁ phase. Erlotinib was approved by the FDA in 2004 for the treatment of NSCLC in patients who have failed front-line chemotherapy and is currently under investigation in the treatment of a variety of solid tumor malignancies, specifically head and neck cancer, non-small cell lung cancer, breast cancer and other squamous cell carcinomas.

Further information can be obtained from the Investigators brochure and package insert.

1.5.1 Nonclinical Pharmacology

Erlotinib directly and reversibly inhibits the human EGFR tyrosine kinase with an IC₅₀ of 2 nM (0.79 ng/mL) in an *in vitro* enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC₅₀ of 20 nM (7.9 ng/mL). This potent inhibition is selective for the EGFR tyrosine kinase both in assays assessing the effects of erlotinib on a variety of other isolated tyrosine kinases and in cellular bioassays designed to isolate this functional pathway. Erlotinib is designed to inhibit EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell cycle progression in the G₁ phase. Oral administration of OSI-774 in mice results in a >70% reduction in EGFR (HER-1) autophosphorylation in human xenografts. Marked growth inhibition of HN5 (head and neck carcinoma) and A431 (squamous cell carcinoma) xenografts in nude mice has been demonstrated.

Data on drug exposure and anti-tumor responses in human tumor xenograft models (HN5 and A431) were analyzed in order to estimate the plasma concentration of erlotinib associated with anti-tumor activity. Based on these efficacy models, the minimum steady-state plasma concentration targeted for clinical activity in humans is projected to be 500 ng/mL.

1.5.2 Nonclinical Toxicology

Toxicology studies have been performed in mice, rats (up to 6 months), dogs (up to 1 year), and monkeys (1 week). Treatment-related effects observed in at least one species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (necrosis), kidney (papillary necrosis and tubular dilatation), gastrointestinal tract (delayed gastric emptying and diarrhea), and embryo-fetal toxicity. Red blood cell parameters were decreased, and white blood cells (primarily neutrophils) were increased. There were treatment-related increases in ALT, AST and bilirubin; increases in bilirubin were likely caused by a treatment-related impairment of bilirubin metabolism.

1.5.3 Summary of Phase I Findings

Phase I trials of erlotinib have explored both schedule and dose to evaluate the safety, tolerability, and pharmacokinetic profile of the compound. A number of pharmacokinetic trials in healthy subjects have been conducted, along with three classic Phase I trials in patients with advanced cancer. The single-agent maximum tolerated dose (MTD) was estimated to be 150 mg administered once daily. The primary toxicities consisted of diarrhea, rash, nausea, headache, emesis, and fatigue. The only dose-limiting toxicity was diarrhea. This event was dose related and was generally controlled with the addition of loperamide therapy and treatment with erlotinib doses of < 200 mg/day. The appearance of the rash seen in the clinical trials of erlotinib conducted in healthy subjects and cancer subjects has been similar. It was only loosely dose related and was seen commonly at doses of > 25 mg/day. The rash was variable in onset, duration, and severity. The mechanistic basis of the rash remains uncertain; histopathologic examination of biopsies of the rash demonstrated polymorphonuclear leukocyte infiltration and mild epidermal hyperproliferation. In some cases, the rash improved despite continued dosing, and in general, it gradually resolved without sequelae following erlotinib discontinuation. The rash did not result in study discontinuation in cancer subjects in either of the Phase I trials. In the phase I study, 50% of patients developed rash and 86% diarrhea at the recommended phase II dose of 150 mg daily (Hidalgo et al., 2001).

Based on the ocular changes observed in the 12-month toxicology study in dogs, screening and follow-up ophthalmologic examinations were instituted in the Phase I and II trials in cancer subjects. In the weekly dosing study (Study 248-005), the only reported erlotinib-related ocular event was an episode of mild watery eyes. In the daily dosing study (Study 248-004), 1 subject experienced moderate corneal edema/keratitis attributed to wearing contact lenses, although an influence of erlotinib was not discounted. The event resolved with temporary discontinuation of both erlotinib and contact lens use; there was no recurrence of symptoms with erlotinib rechallenge in the absence of continued use of contact lenses. No increased incidence of ocular toxicity related to erlotinib treatment compared to placebo was noted in the randomized phase III trial of carboplatin/paclitaxel +/- erlotinib (see investigator's brochure).

1.5.4 Human Pharmacokinetic Studies

Review of the pharmacokinetic profiles from Studies 248-005 and 248-004 (see Investigator Brochure) revealed dose-related increases in exposure to erlotinib. Exposure to the active metabolite (OSI-420) represented ~10% of the parent compound, with an inter-subject variability in exposure of ~2-fold. Repetitive daily dosing resulted in drug accumulation. The target average plasma concentration for clinical efficacy (500 ng/mL) was achieved at doses of ≥ 100 mg in both the daily (Study 248-004) and weekly (Study 248-005) dosing studies. At the recommended dose of 150 mg/day, the accumulation ratio was 2.5 ± 1.2 , minimum plasma steady-state concentrations averaged $1,200 \pm 0.62$ ng/mL, which is above the IC_{50} (7.86 ng/mL) required to inhibit EGFR in intact tumor cells. The half-life with the recommended 150 mg/day dosing was 24.1 hours.

1.5.5 Phase II Trials: Studies in Subjects with Advanced Cancer

The 150 mg/day dose of erlotinib selected for all subsequent trials was based on pharmacokinetic parameters as well as the safety and tolerability profile of this dose level in Phase I trials in advanced, heavily pretreated cancer subjects. Three Phase II trials of the safety, tolerability, and antitumor activity of erlotinib have been conducted in subjects with advanced, refractory malignancies, including

NSCLC, squamous cell carcinoma of the head and neck, and ovarian carcinoma. Subjects in each of these studies received 150 mg/day of erlotinib. Dose reductions were allowed in the case of intolerance. Diarrhea was treated with loperamide therapy and/or dose reduction. Rash was treated with a variety of agents, including oral and topical antibiotics, corticosteroids, and other agents. Available data from the two reported Phase II trials in NSCLC and head and neck cancer demonstrate objective response rate of 4%–12% (Perez-Soler et al., 2004; Soulieres et al., 2004).

1.5.6 Non–Small Cell Lung Carcinoma

Study 248-1007 enrolled 57 subjects at five centers with progressive, recurrent NSCLC previously treated with a platinum-based chemotherapy regimen. Erlotinib was administered at a daily dose of 150 mg. In this study, enrolled subjects had measurable tumors that expressed at least minimal levels of EGFR (HER-1) as detected by immunohistochemical (IHC) analysis. All 57 subjects were evaluable for antitumor response. Eight subjects (12.3%) achieved an objective response (1 complete response, 7 partial responses; 6 were confirmed at Week 12 and beyond). The median and 1 year survivals were 8.4 months and 40% respectively (Perez-Soler et al., 2004). A relationship between response and the degree of EGFR (HER-1) over expression has not been established. Rash was observed in 75% of enrolled subjects.

A phase II study of single agent erlotinib in 80 subjects \geq 70 years of age with previously untreated advanced NSCLC has completed accrual within the Dana Farber Partners Cancer Care. Sixty-six are evaluable for response and outcome. The results from the study thus far demonstrate a response rate of 12% (8/66) with an additional 48% (32/66) of subjects achieving stable disease at 2 months after starting treatment. All 8 of the responders have adenocarcinoma. Three of the 5 patients with a partial response who had tumors available for study had a mutation of EGFR. Two of the 14 with stable disease had a mutation of EGFR. The median survival of the elderly patients with NSCLC treated with single agent erlotinib was 10 months.

1.6 Bexarotene (Targretin®)

Bexarotene (Targretin®) is a RXR specific retinoid that has been approved by the FDA for the treatment of cutaneous T-cell lymphoma (CTCL). It has been shown to be effective and well tolerated in phase I or phase II trials for the treatment of lung and breast cancer when used as a single agent or in combination with other chemotherapeutic agents, and is currently undergoing phase III trials (Rigas 2005). The intriguing properties of this compound include downregulation of cyclin D1, and upregulation of PPAR γ in preclinical studies although its antitumor mechanisms are largely unclear.

Further information can be obtained from the Investigators brochure and package insert.

1.7 Rationale for Erlotinib and Bexarotene in Lung Cancer

Bexarotene and erlotinib are currently being explored in combination in several types of solid tumors. Bexarotene has been widely investigated in cancers including non-small cell lung cancer (Yen 2006, Dragnev 2005, Petty 2005). Preclinical models have shown inhibition of lung cancer and enhancement of other therapies (Bissonnette 2006, Hermann 2005, Wang 2006,). Combination therapy with chemotherapy has yielded promising phase II data, but no survival benefit in the phase II setting (Edelman 2005, Tyagi 2005, Bordoni 2005, Gatzemeier 2005, Ramlau 2005, Wakelee 2005,

Bissonnette 2005, Blumenschein 2005, Jassem 2005, Petty 2005). Further investigations in more selected patient populations are needed to further evaluate its efficiency (Hermann 2005, Bissonnette 2005, Yen 2004).

Erlotinib is currently under investigation in the treatment of solid tumor malignancies, specifically head and neck cancer, non-small cell lung cancer, breast cancer and other squamous cell carcinomas.

Both agents are approved for tumors and preclinical data suggest that additivity and/or synergy may be present. Additionally, current trials testing the combination of erlotinib and bexarotene have shown response rates in NSCLC (E. Dmitrovsky, 2005). Investigators from Dartmouth assessed 24 patients with aerodigestive tract cancers, 5 objective response rates were observed and median overall survival was 14.1 months (Dragnev 2005).

1.8 Study Rationale

Retinoids play a critical role in the regulation of cell division, growth, differentiation, and proliferation. Bexarotene (Targretin®), a multi-targeted synthetic rexinoid, has been studied in lung cancer patients in phase I, II and III trials (Miller 1997, Khuri 2001). Median survival has been encouraging in phase I and II. Decreased expression of RXR has been found in lung cancer patient tumors and this has led to a significantly lower overall survival. Cyclin D1 overexpression has been reported in NSCLC and retinoid-class drugs may promote degradation of cyclin D1 via ubiquitination and proteolysis (Petty 2004, Sah 2002, Masuda 2002). Bexarotene has been shown to decrease proliferation of cell lines by interfering with the EGFR signaling pathway making a combination with EGFR-class agents appropriate (Grandis 1996, Fan 2004).

The study rationale is to further investigate the efficacy of combination erlotinib and bexarotene in the treatment of metastatic NSCLC. It has been hypothesized that combining an EGFR inhibitor with a rexinoid would coordinately repress cyclin D1 expression and thereby confer cooperative clinical effects (26, 27)

2.1 STUDY OBJECTIVES

2.2 Primary Objective

The primary objective is to determine the 8 week progression-free survival rate (i.e. disease control rate) in patients with advanced NSCLC who have failed at least one prior chemotherapy regimen.

2.3 Secondary Objectives

The secondary objectives of this study will be to:

- Determine the overall response rate
- Determine the overall survival
- Determine the time to disease progression
- Assess the safety/toxicity of the study treatment

- Assess biomarker modulation in the tumor tissue and serum samples from the treatment
- Assess plasma and intra-tumor concentrations of study treatment

3.1 OVERVIEW OF STUDY DESIGN

This open-label phase II study will treat patients with advanced NSCLC, who have failed frontline therapy, with the combination of erlotinib and bexarotene.

Patients will be placed into this study after registering and enrolling in the BATTLE protocol and having a baseline tumor tissue biopsy. After having a tumor biopsy and profiling of biomarkers completed, patients will be adaptively randomized into one of several biomarker-integrated trials. Patients will then be enrolled into the specific biomarker-integrated trial and followed per protocol.

The primary outcome is progression-free survival at 8 weeks. Secondary outcomes measured will include overall survival, time to disease progression, safety/toxicity, response as well as modulation of biomarker studies.

Patients will receive 4-week cycles of therapy with combination erlotinib and bexarotene, given in the following schedule. Patients will then have re-imaging and re-biopsy (optional) of the tumor performed to assess the effects of the drugs on tumor markers after completing 2 cycles of therapy.

Cycle Number	Erlotinib Dosage (mg/day)	Bexarotene Dosage (mg/m²/day)
1	150	400
2+	150	400

Erlotinib will be administered daily by mouth at 150 mg.

Bexarotene will be administered daily by mouth at 400 mg/m²/day.

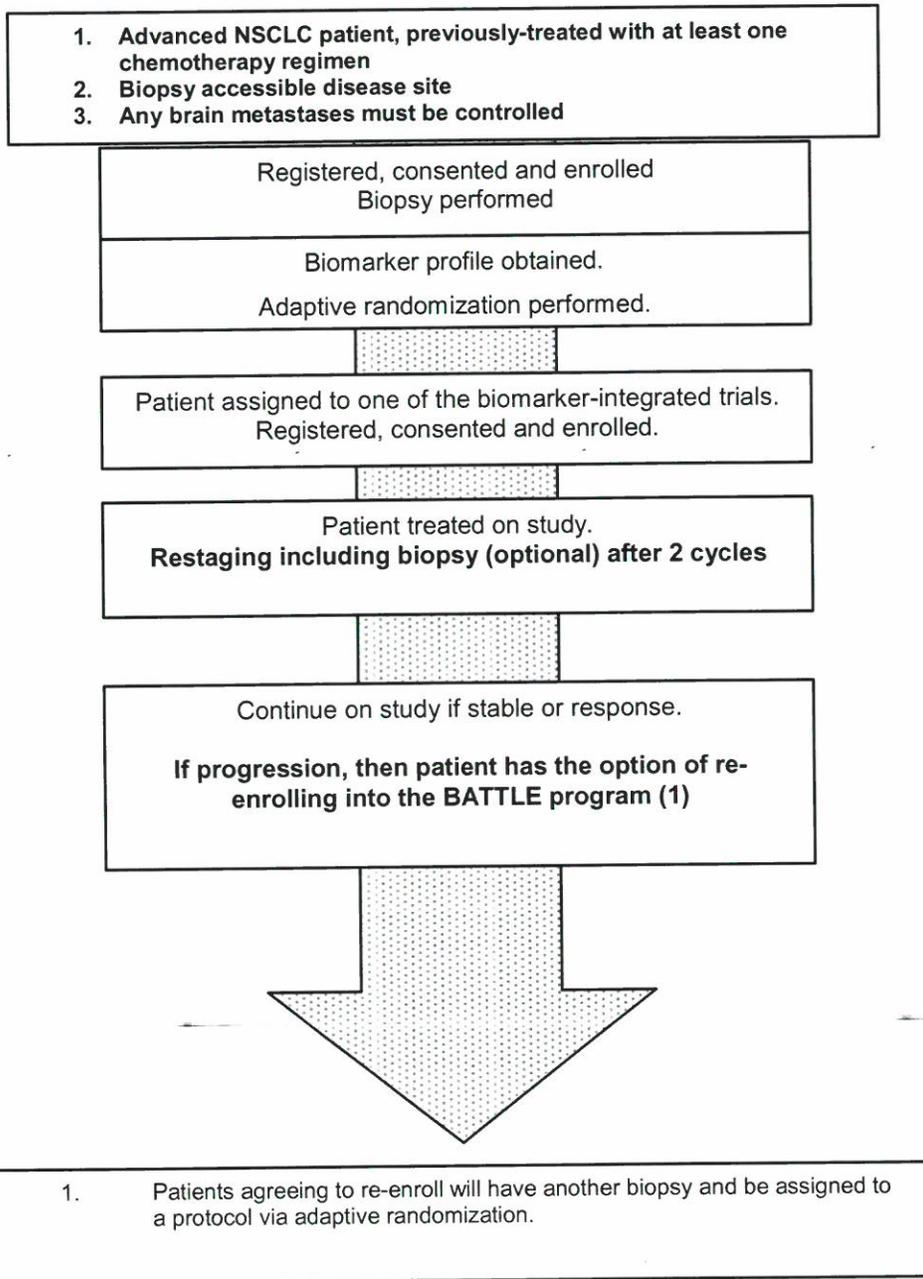
Tumor response will be evaluated after the second cycle of therapy, with confirmation of response 2 cycles after its initial assessment. Patients with no progression of disease (either complete or partial response or stable disease) will continue on therapy. Patients with progressive disease will not be eligible for further treatment on this study and will be allowed to pursue other treatments, including re-entering the BATTLE program and being assigned to another phase II trials. There are no limits to the number of cycles of therapy a patient may receive while on protocol. If a patient, in the absence of progressive disease, experiences intolerable toxicities, the patient will be removed from study.

3.2 Subject Identification

A unique master subject ID will be assigned to each individual participating the study. The subject ID will consist of 5 digits in the format of GG-NNN where GG is the group ID for the institution and NNN

is the accession number within the institution. The unique master ID will be assigned by the central statistical coordinating center at M.D. Anderson. A password protected secured file will be created to store the cross reference list between the master ID and confidential patient information such as name, birth date, hospital number, and social security number (if available), etc. Master ID will be used throughout the trial and in database for patient identification purpose. Confidential patient information will be used only when it is necessary such as in patient care setting.

3.3 Study Schema



4.1 PATIENT SELECTION

All patients enrolling in this study must first be enrolled in the BATTLE umbrella protocol. Unless otherwise indicated, the inclusion and exclusion criteria listed below are identical to those required by the BATTLE protocol.

Patients enrolled in the BATTLE program will be assigned to a specific biomarker-integrated study based on the adaptive randomization model. Patients assigned to this protocol must meet all of the BATTLE eligibility criteria and the eligibility criteria specific to this protocol. If the patient is found to be ineligible for this study, s/he will be assigned to another protocol based on the adaptive randomization model. If a patient participates in this trial and has progressive disease, s/he may re-enter the BATTLE program and be assigned to another phase II study.

4.2 Inclusion Criteria

The following inclusion criteria must be met for entry into the study:

1. The patient has a diagnosis of pathologically confirmed NSCLC by tumor biopsy and/or fine-needle aspiration.
2. The patient has a diagnosis of either stage IIIB, stage IV, or advanced, incurable NSCLC, and failed at least one front-line metastatic NSCLC chemotherapy regimen. (Patients who have failed adjuvant or locally advanced therapy within 6 months are also eligible to participate in study).
3. The patient has uni-dimensionally measurable NSCLC.
4. Karnofsky performance status ≥ 60 or ECOG performance status 0-2
5. The patient has biopsy accessible tumor.
6. The patient has adequate hematologic function as defined by an absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, WBC $\geq 3,000/\text{mm}^3$, and hemoglobin ≥ 9 g/dL.
7. The patient has adequate hepatic function as defined by a total bilirubin level ≤ 1.5 X the upper limit of normal, and alkaline phosphatase, AST or ALT ≤ 2.5 X the upper limit of normal.
8. The patient has adequate renal function as defined by a serum creatinine level ≤ 1.5 mg/dL or a calculated creatinine clearance of ≥ 60 cc/minute.
9. The patient has PT < 1.5 x upper limit of normal
10. If patient has brain metastasis, they must have been stable (treated or asymptomatic) for at least 4 weeks after radiation if treated with radiation and not have used steroids for at least 1 week. Re-imaging performed after 2 weeks, upon completion of radiation therapy.
11. The patient is ≥ 18 years of age.

12. The patient has signed informed consent.
13. The patient is eligible if disease free from a previously treated malignancy, other than a previous NSCLC, for greater than two years. Patients with a history of prior basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix are exempt from exclusion.
14. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Childbearing potential will be defined as women who have had menses within the past 12 months, who have not had tubal ligation or bilateral oophorectomy. Should a woman become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately. The patient, if a man, agrees to use effective contraception or abstinence.
15. Subject must be considered legally capable of providing his or her own consent for participation in this study.

4.3 Exclusion Criteria

The following criteria are grounds for exclusion from this study:

1. The patient has received prior investigational therapy, chemotherapy, surgery, or radiotherapy within 4 weeks of initiating study drug
2. The patient has undergone prior thoracic or abdominal surgery within 28 days of study entry, excluding prior diagnostic biopsy.
3. The patient has received radiation therapy to the measurable tumor within 6 months excluding local irradiation for the management of tumor-related symptoms (bones, brain) and active new disease growing in the previously irradiated site.
4. The patient has a significant medical history or unstable medical condition (unstable systemic disease: congestive heart failure (New York Heart Association Functional Classification class II or worse), recent myocardial infarction within 3 months, unstable angina, active infection (i.e. currently treated with antibiotics), uncontrolled hypertension). Patients with controlled diabetes will be allowed. Patient must be able to undergo procedure for tissue acquisition.
5. The patient has uncontrolled seizure disorder, active neurologic disease, or neuropathy \geq grade 2. Patients with meningeal or CNS involvement by tumor are eligible for the study if the above exclusion criteria are not met.
6. The patient is pregnant (confirmed by serum β -HCG if applicable) or is breastfeeding.
7. Any condition that is unstable or could jeopardize the safety of the patient and its compliance in the study, in the investigator's judgment.
8. The patient is actively taking herbal remedies or over-the-counter biologics (e.g., shark cartilage, high dose antioxidants).

9. Patients will be allowed to have prior biologic (i.e. VEGF, EGFR, etc.) therapy. However, the patient will be excluded from a given study if he/she has received the same therapy as the clinical trial (i.e. If a patient has been previously treated with bevacizumab, they are allowed to enroll in any of the 4 studies. If a patient has been previously treated with erlotinib, they are excluded from the clinical trials with erlotinib). In addition, if a patient has been previously treated with gefitinib (Iressa), they are excluded from the clinical trials with erlotinib.

4.2.1 Additional erlotinib and /or targretin exclusion criteria:

The following are grounds for exclusion from this erlotinib/bexarotene study, but not from the BATTLE umbrella protocol. If a patient meets all BATTLE inclusion and exclusion criteria, but is ineligible due to one of the following criteria, s/he will be reassigned to another phase II BATTLE protocol for which s/he is eligible.

1. The patient has dysphagia and who is unable to swallow intact capsules.
2. The patient has active gastrointestinal disease or a disorder that alters gastrointestinal motility or absorption (i.e., lack of integrity of the gastrointestinal tract such as a significant surgical resection of the stomach or small bowel).
3. The patient has received prior retinoid derivative therapy.
4. The patient has triglycerides >200.

4.3 Study Withdrawal

Patients will be removed from the study for any of the following reasons:

1. Patient requests to withdraw
2. Unwilling or unable to comply with study requirements
3. Identification of recurrent or new cancer
4. Unrelated intercurrent illness that will affect assessment of clinical status to a significant degree as determined by the principal investigator or the treating physician
5. The treating physician or investigator must discontinue study treatment if he/she thinks that the patient's health or well-being is threatened by continuation on study.

If any safety parameters show a clinically significant change from baseline that warrants early termination of treatment, the patient will continue with the scheduled study-related procedures. Appropriate safety monitoring will continue until 30 days after the last dose of the study drug or until adverse events have resolved or returned to baseline. Patients withdrawn from the study will be followed for survival. The reason for and date of the discontinuation will be obtained.

Participants have the right to withdraw from study at any time. If a participant chooses to withdraw, he/she should contact the principal investigator and/or research nurse who will provide any necessary instructions for finalizing removal from study. If the patient requests to withdraw his/her samples (i.e. residual pleural fluid, blood), appropriate personnel will be notified and samples will be withdrawn and destroyed as per UTMDACC Institutional Laboratory Guidelines.

If a patient is non-compliant or lost to follow-up, the research nurse or his/her designee will make three attempts to call the patient over the period of one month. These attempts will be documented. If the research nurse or his/her designee is unable to make contact with either the patient or a family member after three phone calls, then a letter will be sent to the patient's last known address.

5.1 TREATMENT PLAN

All patients enrolling in this study must first be enrolled in the BATTLE umbrella protocol. Unless otherwise indicated, the inclusion and exclusion criteria listed in sections 4.1 and 4.2 are identical to those required by the BATTLE protocol.

We anticipate this study will be activated in September 2006 and will be completed in September 2010.

5.2 Patient Recruitment

MD Anderson Cancer Center (MDACC): Representatives from Thoracic/Head & Neck Medical Oncology (i.e., the principal investigator, the co-principal investigator, sub-investigators, and the research nurse) will screen and evaluate patients seen in the M.D. Anderson Thoracic Center to identify potential subjects. If a patient is outside of the institution, he/she may be directly referred by a physician and/or contact the research nurse directly by phone numbers provided by the website. This study will also be publicized by brochures in the Thoracic clinics and on the MDACC website.

6.1 INVESTIGATIONAL CENTERS

The centers involved include the following: M. D. Anderson Cancer Center. Other centers may be added at a later date.

6.2 Investigator Contact Information

Principal Investigator (MDACC):

Co-Principal Investigators (MDACC):

7.0 Study Conduct

7.1 Patient Enrollment

Patients must be consented prior to any study-related procedures being performed. Once patients are consented for the BATTLE protocol and appropriate procedures are completed, they will be assigned to one of the phase II biomarker-integrated trials via the adaptive randomization model. The patient will then be screened for any additional eligibility criteria that are unique to the phase II trial. If the patient is found to be ineligible for the phase II trial to which s/he was assigned, s/he will be re-assigned to another phase II protocol via the adaptive randomization model.

7.2 IND

The FDA has determined that this study is exempt from IND regulations, and therefore, an IND is not required to conduct the investigation.

8.1 Study evaluations

8.2 Pre-treatment Evaluations

All patients must undergo pre-treatment evaluations within 4 weeks (unless otherwise specified) prior to initiating therapy. Pre-treatment evaluations will be used to determine the patient's study eligibility. Patients must sign an informed consent form prior to undergoing protocol-specific evaluations and prior to receiving treatment:

1. Signed informed consent
2. Biopsy of tumor for biomarker evaluation (Please Note: In some instances (i.e. local irradiation for the management of tumor-related symptoms, surgical procedure, etc.), the length of time from the baseline biopsy and the initiation of study treatment may exceed the 28 day window stated above to allow adequate recovery of study participants prior to study therapy)
3. Medical History: Includes smoking history (duration and intensity).
4. Physical exam: Includes height, weight, performance status assessment, vital signs (pulse, blood pressure, temperature, respiration rate)

5. Chest x-ray within 4 weeks of starting treatment
6. CT or MRI scan of chest within 4 weeks of starting treatment.
7. Brain MRI
8. Serum β -hCG Pregnancy Test—within 48 hours prior to therapy for women of childbearing potential. Childbearing potential will be defined as women who have had menses within the past 12 months, who have not had tubal ligation or bilateral oophorectomy.
9. Hematology Profile—including complete blood count, platelets, and differential
10. Coagulation Profile—PT/INR
11. Chemistry Profile—including total protein, uric acid, blood urea nitrogen (BUN), creatinine, LDH, AST, ALT, alkaline phosphatase, phosphorus, total bilirubin, sodium, potassium, chloride, calcium, albumin, bicarbonate, glucose, and CrCl.
12. Urinalysis—including routine dipstick measurements and a microscopic analysis.
13. Serum biomarker test (optional)
14. Thyroid function tests—including routine T4 and TSH
15. Lipid profile (LDL, HDL, total cholesterol, triglycerides)
16. 12 Lead ECG

8.3 Treatment Evaluations

Patients enrolled in this protocol will also be enrolled in the BATTLE protocol. The following evaluations will be conducted both as a part of this protocol and of the BATTLE protocol in which the patient is enrolled. Each evaluation listed will be conducted once and the information will be used for this protocol and for the BATTLE protocol. All study evaluations and/or clinic visits may be conducted within ± 7 days of the date specified in the protocol.

1. Updated medical history, including current medications, medical conditions, and smoking history (duration and intensity), before each cycle.
2. Physical exam, including weight, performance status assessment, vital signs (pulse, blood pressure, temperature, respiration rate), before each cycle.
3. Tumor tissue biopsy after cycle 2 (optional).
4. PT if patient is undergoing optional tumor tissue biopsy.

5. Chemistry Profile (including total protein, uric acid, BUN, creatinine, LDH, AST, ALT, alkaline phosphatase, phosphorus, total bilirubin, sodium, potassium, chloride, calcium, albumin, bicarbonate, and glucose) before each cycle.
6. Hematology (including CBC with automated differential and platelet count) before each cycle
7. Serum samples for biomarkers will be collected at end of cycles 1, 2 and then every 2 cycles (optional).
8. Chest x-ray after every 2 cycles.
9. CT or MRI scan of chest after every 2 cycles.
10. Thyroid function tests—including routine T4 and TSH before each cycle
11. Lipid profile (LDL, HDL, total cholesterol, fasting triglycerides (at least 10 hours fasting), weekly for weeks 1-4 then every cycle thereafter
12. Patients taking warfarin: INR weekly for first 5 weeks of treatment, then before each cycle.

Visit and Evaluation Timetable

	Baseline	Cycle						End of Treatment
Cycle		1	2	3	4	5	6	
Patient clinic visit	X	X	X	X	X	X	X	X
Physical Examination (including medical and smoking history) ¹	X	X ⁹	X	X	X	X	X	X
Disease Assessment (imaging of disease via CT or MRI, CXR) ²	X		X		X		X	X
Performance Status	X	X ⁹	X	X	X	X	X	X
Brain MRI	X							
ECG	X							
Hematology (CBC,diff,platelets)	X	X ⁹	X	X	X	X	X	X
Coagulation Profile ⁷ (PT and/or INR)	X		X ³					X
Chemistry ⁴	X	X ^{8,9}	X	X	X	X	X	X
T4, TSH	X		X	X	X	X	X	
Lipid Profile with TG	X	Weekly for weeks 1-4	X	X	X	X	X	
Urinalysis	X ⁶							X
Serum Pregnancy Test	X							
Tumor Biopsy	X		X ⁵					
Serum for biomarker analysis, pharmacology study and storage	X ⁵	X ⁵	X ⁵		X ⁵		X ⁵	X ⁵
Survival Assessment								Every 3 months (up to 3 years)

¹ Before every cycle

² After every 2 cycles

³ If patient is undergoing optional tumor tissue biopsy

⁴ Including total protein, uric acid, BUN, creatinine, LDH, AST, ALT, alkaline phosphatase, phosphorus, total bilirubin, sodium, potassium, chloride, calcium, albumin, bicarbonate, and glucose.

⁵ Optional: Only performed if previously consented

⁶ Including routine dipstick measurements and a microscopic analysis.

⁷ For patients taking warfarin, INR weekly for first 5 weeks of treatment, then before each cycle.

⁸ AST and ALT taken at weeks 1, 2, 4, and every cycle thereafter.

⁹ Only performed if previous pre-treatment evaluations are not conducted within 28 days prior to initiating study therapy

8.4 End of Therapy Evaluations

End of therapy evaluations will be assessed for patients who are no longer receiving therapy on protocol. These evaluations will include a physical examination, hematology and serum chemistry profiles, serum for biomarker analysis, urinalysis, imaging, diagnostic studies (if indicated), and tumor response assessments.

8.5 Follow-up Evaluations

Patients will have a follow-up evaluation performed 4 weeks after therapy is discontinued. This evaluation may be a visit or contact by the research personnel. Patients will be contacted every 3 months to collect survival information (for up to 3 years).

9.1 STUDY PROCEDURES/TESTS

9.2 Tumor tissue biopsy

Tissue biopsies will be performed at baseline and at 2 cycles (optional) while participating in the study. In addition, archival diagnostic tissue samples will also be collected for biomarker analysis (See Appendices C and E for detailed biomarker analysis and processing procedures). Tissue may be obtained via CT-guided core biopsy, bronchoscopy, or other core biopsy methods to available tissue (i.e. subcutaneous or cutaneous or lymph node disease).

1. Bronchoscopy: Study subjects will undergo autofluorescence and white-light bronchoscopy after being NPO in regard to solid food for a minimum of six hours and NPO for oral medications and small amounts of liquids for two hours prior to the procedure. Subjects will be advised to discontinue any anticoagulation medications prior to procedure according to standard current guidelines (See Appendix K). The participant will be monitored with continuous electro-cardiographic, respiratory, and oximetric monitoring, with intermittent blood pressure monitoring. A endobronchial inspection will be performed and at least 2 core biopsies of the tumor will be performed. Specimens will be used to analyze biomarkers, genomic, proteomic, and other biomarker studies.

2. CT-guided core biopsy: Study subjects will undergo CT-guided core biopsy after being NPO in regard to solid food for a minimum of six hours and NPO for oral medications and small amounts of liquids for two hours prior to the procedure. Subjects will be advised to discontinue any anticoagulation medications prior to procedure according to standard current guidelines (See Appendix K). The participant will be monitored with continuous electro-cardiographic, respiratory, and oximetric monitoring, with intermittent blood pressure monitoring. At least 2 core biopsies of the tumor will be performed. Specimens will be used to analyze biomarkers, genomic, proteomic, and other biomarker studies.

9.3 Serologies (Optional)

Consenting participants will have blood collected at baseline and cycles 1 and 2, then every 2 cycles, and at disease progression while participating in the BATTLE program. The blood samples are optional and participants are not required to provide them. The collected blood specimen will be processed, stored, and analyzed for biomarker, genomic and proteomic studies as well as gene expression profiles (see section 9.3 and Appendices C and E for detailed analysis and processing procedures).

9.4 STUDY CORRELATES

9.4.1 Collection of Serum Samples, Processing, and Analysis (optional)

BLOOD SAMPLE COLLECTION TIME POINTS:

- 1) Baseline: Prior to start of therapy
- 2) End of Cycle 1 – Day 28
- 3) End of Cycle 2 – Day 56
- 4) Every 2 cycles after the first 2 cycles
- 5) Disease Progression

9.3.1.1 Serum Collection and Processing

At each time point, venous blood (8 mL) will be taken into tubes containing lithium heparin anticoagulant (Vacutainer®) and thoroughly mixed. Samples will be clearly labeled by the laboratory with the study number and the sample identification number (see the following section titled “Labeling”). If possible, the blood samples will then be centrifuged within 30 minutes of collection at 1500 RPM x 15 minutes @ 5°C. Plasma is removed & stored in properly labelled cryovials. All specimen is to be stored at -70°C until analysis.

9.4 Pharmacology Study – Dr. Hai Tran

Bexarotene belongs to a subclass of retinoids that selectively activate retinoid X receptors (RXRs), thereby inhibiting growth and inducing regression of some tumor cell lines (hematopoietic and squamous cell origin). The biologic activity of the RXRs is different from that of retinoic acid receptors (RARs). The recommended initial oral dose is 300 milligrams/square meter (mg/m²) daily with a meal, which can be modified up to 400 mg/m² with careful monitoring. Oral doses of 500 to 650 mg/m² daily have been administered in cutaneous T-cell lymphoma. Peak plasma levels of bexarotene occur 2 to 4 hours after oral administration; the elimination half-life is 1 to 7 hours. With a soft gelatin capsule formulation, peak plasma levels of 5, 12, and 44 ng/mL were observed with doses of 5, 20, and 40 mg, respectively. Peak levels occurred 2.4 to 4.7 hours postdose (Miller et al, 1997). With a micronized formulation of bexarotene (Ligand Pharmaceuticals), significantly higher plasma levels are achieved. After oral doses of 18, 50, 140, 300, and 400 mg/m² of this formulation, peak plasma levels were 67, 307, 517, 911, and 1890 ng/mL, respectively. . AUC values are approximately 3000 and 8000 ng x hr/mL after 300- and 400-mg doses of the micronized formulation (Miller et al, 1997). Significant inpatient and outpatient variability in plasma levels was reported. Specific data

are lacking. A 10-fold or greater increase in bioavailability is seen with the micronized formulation compared to conventional soft gelatin capsules (Miller et al, 1997).

Bioavailability is significantly increased with food (Prod Info Targretin(R) capsules, 2000). Administration of bexarotene 300 mg/m² after a fat-containing meal resulted in a 35% increase in AUC and a 48% increase in peak plasma concentrations when compared with these values following administration of bexarotene with a glucose solution (Prod Info Targretin(R) capsules, 2000). The manufacturer recommends administration of bexarotene with a meal. Protein binding is greater than 99%, and less than 1% of the drug is excreted in urine. The presence of hepatic impairment can significantly reduce bexarotene clearance. Autoinduction of metabolism has not been observed after oral doses in limited studies. Cytochrome P450 3A4 is suggested by in vitro studies to be the major cytochrome P450 responsible for formation of the oxidative metabolites. Oxidative metabolites may be glucuronidated. The oxidative metabolites are active in in vitro assays of retinoid receptor activation. (6- and 7-hydroxy-bexarotene, 6- and 7-oxo-bexarotene).

The epidermal growth factor receptor, EGFR (erbB-1/HER1), is the prototypic member of the erbB/HER family of cell-surface receptors, which are involved in cell growth and differentiation (Adjei, 2001; Ciardiello & Tortora, 2001). Erlotinib (OSI-774) is a quinazoline derivative with selective epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor. It is a specific, reversible, and ATP-competitive inhibitor of tumor-cell EGFR (erbB-1) tyrosine kinase (50% inhibitory concentration of 2 nM) and EGFR autophosphorylation (15 to 20 nM) (Allen et al, 2000; Hidalgo et al, 2001; de Bono & Rowinsky, 2002). The binding site of erlotinib has been demonstrated to be the intracellular kinase domain of the EGFR (Adjei, 2001). The activity of erlotinib against EGFR tyrosine kinase is at least 1000-fold that of other human kinases (eg, c-src) (Hidalgo et al, 2001). It is about 10 times as potent as gefitinib (de Bono & Rowinsky, 2002).

In vitro, erlotinib has inhibited growth of numerous EGFR-expressing tumors, secondary to cell-cycle arrest in G1 and apoptosis (Hidalgo et al, 2001; Allen et al, 2000; Adjei, 2001). In one in vitro series of human tumor cells from patients, responses (inhibition) were seen in 63%, 75%, and 83% of breast, non-small-cell, and ovarian cancer specimens, respectively, at a concentration of about 10 micromols/liter (L) (Allen et al, 2000). Significant in vivo activity has been reported in human tumor xenografts with various oral/intraperitoneal doses (Ciardiello & Tortora, 2001; Hidalgo et al, 2001; de Bono & Rowinsky, 2002).

In mice bearing human head and neck tumor xenografts, 90% inhibition of EGFR autophosphorylation was seen about 1 hour after an oral dose of 100 milligrams/kilogram (mg/kg); autophosphorylation was reduced by 80% for approximately 12 hours after dosing (Hidalgo et al, 2001). Maximum inhibition of EGFR autophosphorylation was evident 1 hour following a 100-mg/kg oral dose of erlotinib (Hidalgo et al, 2001). In animal models, EGFR autophosphorylation was decreased by about 75% for at least 12 hours following a 100-mg/kg oral dose of erlotinib; total recovery of EGFR function was observed 24 hours after dosing (Hidalgo et al, 2001). These findings were the basis for a protracted daily oral administration schedule

With limited pharmacokinetic data, peak plasma levels of erlotinib occur about 3 hours after an oral dose in cancer patients; a volume of distribution of 136 liters (L), clearance of 6 L, and elimination half-life of 24 hours were observed after single oral doses. Erlotinib is metabolized in the liver, primarily to an O-demethylated derivative (OSI-420), which is active. In animal studies, an oral bioavailability of 80% has been reported.

After single or multiple oral doses of 25 to 200 mg (daily) in cancer patients, times to peak plasma levels ranged from 2 to 12 hours in one study (median, 3 hours); peak levels were approximately proportional to dose. With 150-mg once daily dosing, mean peak levels on day 1 (first dose) and day 28 were 1.2 mcg/mL and 1.7 mcg/mL, respectively; the minimum (trough) plasma level on day 28 was 1.2 mcg/mL (Hidalgo et al, 2001). Erlotinib was highly protein-bound in animal studies (90 to 95%) (Hidalgo et al, 2001).

Data from preclinical (animal) studies suggest that a plasma level of 0.5 mcg/mL provides significant epidermal growth factor receptor (EGFR)-tyrosine kinase inhibition and antiproliferative activity (Hidalgo et al, 2001; de Bono & Rowinsky, 2002). Steady-state trough plasma levels in most cancer patients have exceeded 0.5 mcg/mL during oral administration of 150 mg once daily; in contrast, this level was only occasionally sustained with lower doses (ie, 50 or 100 mg daily) (Hidalgo et al, 2001).

Objectives:

- 1) To determine individual patient's plasma concentrations of erlotinib (Tarceva) and bexarotene (Targretin) at steady-state.
- 2) To determine individual patient's intra-tumor (if available) concentration of erlotinib (Tarceva) and bexarotene (Targretin).
- 3) To determine, if any correlation exist between circulating plasma and intra-tumor (if available) concentrations and degree of response and toxicities using pharmacokinetics and pharmacodynamic modeling

Labeling

Plasma and tumor samples will be clearly labeled, by the appropriate site personnel, with the following information:

1. Protocol Study Number, Site ID, Subject Study number, date of sample, visit number, cycle number and nominal time (day and time-point where appropriate) and the sample collection time.

It is essential that the following information be recorded:

- The date and actual time the blood sample was taken
- The date and time the doses were taken for at least two days immediately before each visit when the sample is collected

Analysis of PK Samples

Processing and analysis of plasma and tumor (if available) samples will be performed by Dr. Hai T. Tran's Laboratory at UTMDACC using validated LC/MS/MS method.

9.5 PBMC isolation for circulating endothelial cells and monocyte assays - Dr. John Heymach

PBMCs will be isolated before therapy, at end of cycle 1, at end of cycle 2, and every other cycle thereafter, and at the time of disease progression or termination from the study for other reasons. Approximately 7 ml of venous blood will be collected into a Vacutainer CPT tube with sodium citrate (Becton Dickinson, San Jose, CA). The tube will be gently inverted several times to ensure

mixing with the anticoagulant, and within 2 hours, the tube will be centrifuged at room temperature in a horizontal rotor for 25 minutes at 1,600 g. After centrifugation, the mononuclear cells will be visible in a whitish layer just under the plasma. We will remove 1 ml of the plasma (top layer) and put it into cryotube 1. We will then remove the mononuclear layer (1.5 ml) and put it into cryotube 2 and transfer half of the mononuclear cells (0.75 ml) into cryotube 3. A total of 0.75 ml of freezing medium (RPMI 1640 medium with 20% dimethyl sulfoxide) will be added to each of the PBMC cryotubes (tubes 2 and 3). All three cryotubes will immediately be placed in a -80°C freezer. Samples will be stored at -70°C to -80°C .

Analysis of CECs and other PBMC populations will be performed by four-color flow cytometry at the University of Texas M.D. Anderson Cancer Center. Briefly, analysis will be conducted with using a panel of antibodies to identify different cellular populations such as: CD146 as a marker of mature ECs; CD133 as a marker of EC precursors; CD45 to exclude hematopoietic cells; and anti-KDR as a marker of both precursor and mature endothelial cells (Beaudry 2005). Apoptosis markers (i.e. annexin V) will also be incorporated. Standard analysis gates will be used to exclude dead cells and platelets. The number of mature CECs, expressed as a percentage of PBMCs, will be recorded and the absolute number of CECs and CEPs (number per microliter of blood) will be derived using the patients white count and differential.

10 EVALUATION CRITERIA

10.1 Safety

The safety of the investigational study agent will be determined via safety evaluations consisting of reported adverse events, physical examinations, tumor-related symptom assessments, vital signs, and laboratory analyses.

An adverse event will be defined as any unfavorable and unintended sign, including a significant abnormal laboratory finding, symptom, or disease, whether or not related to the investigational study agent.

A tumor-related symptom will be defined as any subjective and/or objective evidence of NSCLC.

Systemic and local adverse events will be assessed using established Common Toxicity Criteria (CTC) version 3.0. For adverse events not contained within the Toxicity Criteria, the Principal Investigator will be responsible for assessing the severity of an adverse event based on the jeopardy to the patient's health and well being, and the ability of the patient to function during the event. These adverse events will be graded as mild, moderate, severe, or life-threatening, and will be followed until resolution or stabilization.

10.2 Tumor Response

The initial tumor response (uni-dimensionally measured disease) will be assessed at the completion of two cycles of therapy, and will be compared to pre-treatment values. Subsequent tumor response for patients receiving therapy will be assessed following the completion of every two cycles of therapy. Responses will be based on a comparison to the pre-treatment tumor evaluation via chest x-ray and

CT or MRI. All patients who have received treatment with at least one cycle of treatment will be considered evaluable for response. Imaging and diagnostic studies of measurable and evaluable tumors should be repeated following every two cycles of therapy. (See Appendix Response Evaluation)

NOTE: The pre-treatment and all subsequent imaging and diagnostic studies should be obtained from the same source, for example, chest x-ray and CT scan or MRI. Each response parameter will be reported independently. Responses are to be scored based on measurable and nonmeasurable criteria and overall response to therapy.

11 STUDY MEDICATIONS

11.1 Bexarotene (Targretin®)

11.1.1 How Supplied

Bexarotene (Targretin®) capsules for oral administration will be supplied as follows:

75 mg capsules: Off-white, oblong, soft gelatin capsules in bottles and imprinted with "Targretin." Active

Ingredient: Bexarotene

Chemical Name: 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl]-benzoic acid

Molecular Weight of Bexarotene: 348.48

Other Names for Drug Substance: LGD1069, LG100069

Excipients: Each capsule contains polyethylene glycol 400 NF, polysorbate 20 NF, povidone USP, and butylated hydroxyanisole NF. The capsule shell contains gelatin NF, sorbitol special-glycerin blend, and titanium dioxide USP.

Solubility: Bexarotene is insoluble in water and has limited solubility in vegetable oils and ethanol.

Source: Ligand Pharmaceuticals

11.1.2 Packaging, Labeling and Dispensing

The study staff will compute the body surface area (BSA) from each patient's height and weight using a body surface area nomogram. The calculated absolute dose will be determined by multiplying the BSA in m^2 by the assigned mg/m^2 dose regimen. The amount of the total once-daily dose in mg to be administered should be computed to within the nearest 37.5 mg, using the appropriate number of 75 mg capsules. Details of dosing information (e.g., BSA, prescribed dose, date of dosing, any dose adjustments) are to be captured in the case report forms.

At each visit, the appropriate number of bexarotene capsules sufficient for continuation of treatment until the next scheduled visit will be dispensed to the patient. In general, the quantity dispensed should not exceed one month of treatment except as necessary because of the indivisible packaging consisting of 100 capsules per bottle. The capsules must be dispensed in Ligand's containers to assure stability of the drug.

At each visit at which bexarotene capsules are dispensed and at the conclusion of the study, patients must be instructed to return all unused capsules in partially or completely full bottles in order to adequately assess each patient's compliance with dosing instructions. Capsule counts should be compared to the amount of study drug the patient should have taken in the preceding study interval. Empty medication bottles must also be returned for accounting. When the patient returns capsules or bottles, the date of return will be recorded on the Drug Inventory Form. Every effort should be made to obtain return of all unused capsules and dispensed bottles. If such effort fails, a dated note explaining the reason for the failure to collect the drug should be made on the Drug Inventory Form.

Returned bottles should not be re-dispensed to the patient at any time. At each visit at which bexarotene capsules are dispensed, a new supply of study drug should be provided to the patient.

11.1.3 Bexarotene Administration

Bexarotene capsules should be taken with or immediately after a meal. Patients should swallow each capsule whole. The capsule should not be chewed, crushed, or dissolved in liquid.

11.1.4 Storage Requirements

Patients should be instructed to store their bottles of bexarotene capsules with the caps tightly closed in a safe area at 2° to 25° C (36° to 77° F). Bexarotene capsules should not be stored near heating devices, high temperatures or humidity, or where children or pets have access to them. Bexarotene capsules should be protected from sunlight.

11.1.5 Bexarotene Monitoring and Treatment Alterations

Hypothyroidism

Bexarotene capsules have been associated with central hypothyroidism. In the Phase II-III studies in patients with CTCL, Bexarotene capsules induced biochemical evidence of clinical hypothyroidism in about half of all patients treated, causing a reversible reduction in thyroid hormone (total thyroxine [total T4]) and thyroid stimulating hormone (TSH) levels. The incidences of decreases in TSH and total T4 were about 60% and 45%, respectively, in patients treated at the recommended initial dose of 300 mg/m²/day. Biochemical hypothyroidism was not always associated with clinical symptoms and/or might have been associated with symptoms that were not readily attributed to hypothyroidism but may have been attributed to the underlying disease. The incidence of hypothyroidism reported as an adverse event in these studies was 29%. A total of 37% of patients received treatment with thyroid hormone replacement. The central hypothyroidism was reversible, with recovery to normal levels of TSH occurring as early as seven days after discontinuation of Bexarotene capsules.

In this current study, TSH and free T4 levels are obtained at baseline (Day 1); the T4 level is repeated every four weeks until discontinuation of Bexarotene capsules. It is anticipated that most of the effect on the thyroid will be realized within the first four weeks of bexarotene treatment. The Investigator is encouraged to be alert for emerging early symptoms of hypothyroidism, such as fatigue and cold

intolerance. Treatment with thyroid hormone supplements should be considered in patients with laboratory evidence of hypothyroidism. Failure to treat hypothyroidism may exacerbate the side effect of hypertriglyceridemia and render control of elevated triglyceride levels more difficult.

The dose of thyroid hormone required to treat patients with bexarotene-induced hypothyroidism in other clinical trials did not differ substantially from the dose required to treat hypothyroidism from other causes. Because the hypothyroidism observed in association with bexarotene is central in nature, the dose required to render the patient euthyroid should be guided by the normalization of the free T4 level and cannot be guided by the suppression of TSH.

Hypertriglyceridemia and/or Hyperlipidemia Management

Bexarotene capsules have been associated with altered blood lipid profiles, especially increased serum triglycerides. Significant elevation of serum triglyceride levels is associated with an increased risk for developing acute pancreatitis, especially in the presence of other risk factors for pancreatitis (e.g., prior history of pancreatitis, uncontrolled hyperlipidemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity).

In the Phase II-III studies, about 70% of patients with cutaneous t-cell lymphoma (CTCL) who received Bexarotene capsules at an initial dose of ≥ 300 mg/m²/day had fasting triglyceride levels greater than 2.5 times the upper limit of normal. About 55% had values over 800 mg/dL. Cholesterol elevations above 300 mg/dL occurred in approximately 60% and 75% of patients with CTCL who received an initial dose of 300 mg/m²/day or >300 mg/m²/day, respectively. Decreases in HDL cholesterol to less than 25 mg/dL were seen in about 55% and 90% of patients at these initial dose levels, respectively. The effects of triglycerides, HDL cholesterol, and total cholesterol were reversible with cessation of therapy, and could generally be mitigated by dose reduction or concomitant antilipid therapy.

Acute pancreatitis, in association with serum triglyceride levels exceeding 770 mg/dL, has been reported in about 2% of patients receiving Bexarotene capsules; however, these patients were not on aggressive treatment with Lipitor and levothyroxine. If fasting triglycerides are elevated during Bexarotene capsule treatment, antilipid therapy should be adjusted and, if necessary, the dose of Bexarotene capsules should be reduced or suspended.

Fasting triglycerides must be within the age-adjusted normal limit or normalized with appropriate intervention prior to initiating Bexarotene capsule therapy. Treatment with atorvastatin (Lipitor) or equivalent antilipemic agent must be initiated on or before Day 1. Antilipemic therapy may need to be escalated rapidly in the presence of persistent hypertriglyceridemia to avoid decreasing bexarotene dose. Gemfibrozil (Lopid®) should not be used in conjunction with Bexarotene capsules because of a documented drug-drug interaction that increased plasma levels of bexarotene and made the control of hypertriglyceridemia difficult.

In general, it is recommended that fasting lipid determinations should be performed post-baseline no less frequently than at weekly intervals until the lipid response to Bexarotene capsules is established, which usually occurs within two to four weeks, and then at four-week intervals thereafter. For this reason, this protocol specifies that post-baseline fasting lipid determinations should be performed weekly until Week 4, and then every four (4) weeks thereafter throughout the time of the follow-up visit

that is to occur approximately four weeks after discontinuation of Bexarotene capsules. Attempts should be made to maintain serum triglyceride levels below 800 mg/dL.

Atorvastatin (Lipitor) has been used effectively to control bexarotene-induced hypertriglyceridemia. In Phase II-III clinical trials of Bexarotene capsules in patients with refractory or persistent CTCL, atorvastatin was used by 48% (73/152) of patients. In an interim analysis of data from a Phase II clinical trial of Bexarotene capsules in patients with metastatic breast cancer, fenofibrate was the recommended antilipid agent and antilipid therapy was initiated for 67% (52/90) patients.

If the patient has triglyceride levels at screening that are not within the age-adjusted norm, the patient should begin on Lipitor 40 mg qd and monitored until the triglyceride levels have normalized. Once the triglyceride levels have been normalized, the patient may be entered into the study.

After the first week of Bexarotene treatment, the triglycerides should be measured. If the triglyceride level is 400-800 mg/dL, the Lipitor dose should be increased to 80 mg/d. If the triglyceride level is 800-1200 mg/dL, the Lipitor dose should be increased to 80 mg daily and a Bexarotene dose reduction to 300 mg/m² should be considered. If the triglyceride level is greater than 1200 mg/dL, the Bexarotene should be held for one week and restarted at a dose of 300 mg/m². Antilipemic therapy may need to be escalated rapidly in the presence of persistent hypertriglyceridemia to avoid decreasing bexarotene dose. The triglyceride levels should be measured at Weeks 2, 3, and 4. If the triglycerides are not controlled, modify the Lipitor and Bexarotene doses as described above. If the LFT's are greater than three times the upper limit of normal, the Lipitor should be discontinued and the Bexarotene dose should be reduced.

Patients should be regularly reminded to avoid risk factors that can lead to pancreatitis, such as heavy alcohol consumption and/or dehydration. Additionally, patients should be cautioned to be alert for any symptoms suggestive of the onset of pancreatitis, such as abdominal pain, nausea and vomiting.

11.2 Erlotinib (Tarceva™)

Erlotinib (OSI-774, Tarceva™) is supplied by OSI Pharmaceuticals, Melville, NY, in partnership with Genentech. Erlotinib is FDA approved for treatment of locally advanced or metastatic non-small cell lung cancer after the failure of at least one prior chemotherapy regimen.

11.2.1 Drug Accountability

All study drug required for completion of the study will be provided by OSI Pharmaceuticals, Inc. The recipient will acknowledge receipt of the drug by returning the drug receipt form indicating shipment content and condition. Damaged supplies will be replaced. Study drug accountability records should be maintained by the site in accordance with the regulations.

The original drug supply request of erlotinib will be submitted to Genentech along with the form "Approval for Drug Re-Supply", indicating which personnel will be able to submit drug re-supply requests. All subsequent drug re-supply requests will be directly submitted to OSI-Pharmaceuticals from the site.

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs, or returned to the OSI-Pharmaceutical Drug Depot.

11.2.2 Formulation, Packaging and Storage

Erlotinib oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. In addition to the active ingredient, erlotinib, tablets contain lactose, hydrous microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate. Study drug for daily oral administration will be supplied as 25, 100, and 150 mg tablets of erlotinib, in white, high-density polyethylene (HDPE) bottles with child-resistant closures and should be stored at temperatures between 15°C and 30°C (59°F and 86°F). For further details, see the erlotinib Investigator Brochure. 11.2.3 Storage Requirements

11.2.3 Preparation and Administration

Tablets should be taken preferably in the morning one hour prior or two hours after a meal with up to 200 mL of water. Each bottle will contain 30 tablets, a quantity sufficient for 4 consecutive weeks of dosing, with overage. Subjects who are unable to swallow tablets may dissolve the tablets in distilled water for administration. If a subject forgets to take a dose, the last missed dose should be taken as soon as the subject remembers, as long as it is at least 12 hours before the next dose is due to be taken. The daily treatment schedule will be resumed the next day with the subject taking their scheduled dose at their usual time. In subjects who have emesis and are unable to retain erlotinib for 30 minutes or longer, every attempt should be made to obtain control of nausea and vomiting. The dose of erlotinib may be repeated if emesis occurs within 30 minutes of taking the tablet.

11.2.4 Erlotinib Warning and Precautions

Based upon clinical experience to date, the following adverse effects may be associated with Erlotinib administration: The primary toxicities consist of diarrhea, rash, nausea, vomiting, stomatitis, headache, and fatigue. The only dose-limiting toxicity observed to date is diarrhea. This event is dose-related and is generally controlled with the addition of loperamide therapy, starting doses of erlotinib of < 200 mg/day, and dose reductions.

Rash occurred in 75% of erlotinib-treated NSCLC patients enrolled in BR.21. A papular, pustular rash manifesting most often on the face and upper trunk was common across all studies, but rash was rarely the cause of study drug discontinuation. The rash may be associated with erythema, pain, pruritus, dryness, and less commonly, stomatitis, keratitis and nailbed changes. Wearing of contact lenses while receiving erlotinib therapy is not recommended. The incidence of diarrhea in BR.21 was 54% of erlotinib-treated NSCLC patients. The median time to onset of skin rash was 8 days and median time to occurrence of first diarrheal symptom was 9 days.

There have been infrequent reports of serious (including fatal) interstitial lung disease (ILD) in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumors. In Study BR.21, the incidence of ILD (0.8%) was the same in the placebo and erlotinib groups. The overall incidence in erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Included in this rate of ILD are reported diagnoses of pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, and lung infiltration, irrespective of investigator assessed causality. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, preexisting parenchymal lung disease, metastatic lung disease, or pulmonary infections.

Reversible renal impairment has been reported in association with dehydration associated with nausea, vomiting, and diarrhea. There have been rare reports of renal failure in patients receiving erlotinib in combination with platinum-containing chemotherapy regimens. Febrile neutropenia has been reported in patients receiving concomitant chemotherapy.

Erlotinib is both protein bound (92%–95%) and metabolized by hepatic cytochromes CYP3A4 and CYP3A5 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 inhibitors/inducers.

Co-administration of erlotinib with an inhibitor of CYP3A4 metabolism (ketoconazole, 200 mg po BID for 5 days) resulted in increased exposure to erlotinib as measured by an 86% increase in median erlotinib AUC and a 69% increase C_{max} , compared with administration of erlotinib alone. Induction of CYP3A4 metabolism by a known enzyme inducer (rifampin, 600 mg po QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, compared with administration of erlotinib alone. However, the effect of rifampin on C_{max} was negligible.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on erlotinib.

Additional rare side effects have included: interstitial pneumonitis, gastrointestinal irritation including gastrointestinal perforation, increased risk of gastrointestinal bleeding when combined with NSAIDs, stomatitis, anorexia, alopecia, pruritis, myalgias, bone pain, cough, dyspnea, and ocular changes. For complete details of these rare side effects please see the IND safety reports and erlotinib Investigator's brochure.

11.2.5 Treatment of Erlotinib Toxicity and Dose Modification

This study will utilize the Common Toxicity Criteria (CTC) version 3.0 for toxicity and Adverse Event reporting. A copy of the CTC version 3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). All treatment areas have access to a copy of the CTC version 3.0.

All toxic effects will be managed symptomatically, as indicated. Toxicities will be graded using the NCI Common Toxicity Criteria. Dose adjustments will be made as follows:

Dose reduction or interruption of study drug for adverse events may take place at any time during the study. Toxicity is based on NCI-CTC, Version 3.

Management of a tolerable Grade 2 or 3 rash should include continuation of erlotinib at the current dose and symptomatic management. Because secondary bacterial infections are common and can lead to more serious complications, topical or systemic antibiotics may be considered. Anecdotally, topical or a short course of systemic corticosteroids can be helpful. If skin rash persists or worsens over 10–14 days, dose reduction according to Table 2 should be considered. When skin toxicity improves by at least one grade level, the dose may be re-escalated as tolerated. In Phase II trials, this approach enabled dose re-escalation for the majority of patients requiring dose reduction for skin toxicity. Patients experiencing Grade 4 skin toxicity should be discontinued from the study.

For Grade 1 or 2 diarrhea, early intervention should include continuation of study drug at the current dose and initiation of loperamide therapy as described in **Table 3**. Persistent Grade 2 diarrhea, despite optimal medical management over 48–72 hours, should be managed by dose reduction according to **Table 2**. Patients should be maintained at the reduced dose without attempt at dose re-escalation. Patients experiencing Grade 3 diarrhea should interrupt study drug until resolution to Grade ≤ 1 and restart at a reduced dose according to **Table 2**. Patients experiencing Grade 4 diarrhea should be discontinued from the study.

Patients who experience Grade 3 fatigue should be managed with a dose reduction of 150mg to 100mg. Patients who experience Grade 4 fatigue should be discontinued from study.

Other serious adverse events or Grade 3 or 4 adverse events considered to be related to study drug should be managed with dose interruption until resolution of the event (Grade ≤ 1). Other serious adverse events or Grade 3 or 4 adverse events not resolving in 2 weeks will result in patient discontinuation. Patients may be rechallenged with study drug at the same dose level if the criteria for rechallenge are met. If the adverse event recurs after rechallenge, the patient should be withdrawn from the study.

Although quite rare, interstitial lung disease (ILD) can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often provided. Erlotinib should not be restarted in those patients suspected of having drug-related ILD.

Table 2: Erlotinib Dose Level Reductions

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

Within 2 weeks following a dose interruption or reduction, study drug–related toxicity must improve by at least one grade and be Grade ≤ 1 , or further dose reduction by one level will be required. Dosing may be interrupted for a maximum of 2 weeks if clinically indicated and if the toxicity is not controlled by optimal supportive medication. No more than two dose reductions will be allowed.

Table 3 outlines study drug dose modification criteria for study drug–related toxicities as well as guidelines for their management.

Table 3
Dosage Modification Criteria and Guidelines for Management
of Erlotinib-Related Toxicities

NCI-CTCAE (v 3.0) Grade	Erlotinib Dose Modification	Guideline for Management
Diarrhea		
Grade 1	None	Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours)
Grade 2	None (Dose reduction of erlotinib is necessary if diarrhea persists over 48–72 hours despite optimal medical management)	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours)
Grade 3	Interrupt then dose reduce erlotinib. Erlotinib should not be re-escalated.	Interrupt erlotinib until resolution to Grade ≤1, and restart at next reduced dose
Grade 4	Discontinue study treatment.	
Pulmonary Events if possibly ILD		
All Grades	Temporarily interrupt erlotinib pending the diagnostic evaluation. If the pulmonary adverse event is assessed as related to erlotinib, discontinue the patient from study treatment.	Unexplained dyspnea, either new or progressive, should be aggressively evaluated.
Rash		
Tolerable rash (Grade 2 or 3)	None	Any of the following: minocycline ^a , topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course) at discretion of investigator
Intolerable rash (Grade 2 or 3)	Consider interruption and or dose reduction if unresponsive to symptomatic management. Re-escalation is allowed.	Manage as described above
Grade 4	Discontinue study treatment.	Manage as described above

^a Recommended dose: 200 mg po bid (loading dose) followed by 100 mg po bid for 7–10 days.

11.3 Handling, dispensing, and storage of study drugs

Study drug supplies must be stored in a secure, locked area. Bexarotene and erlotinib must be dispensed only from official study sites by authorized personnel according to local regulations. Drugs should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study patients. Unless otherwise instructed by Ligand Pharmaceuticals and/or OSI Pharmaceuticals in writing, the Institution will destroy any supplies of bexarotene and/or erlotinib that expire during this study. The Institution will destroy these materials in accordance with all applicable regulations and governmental guidelines and institutional policies.

At the conclusion of this study, all unused drug will be destroyed at the study site according to institutional procedures.

12 CONCOMITANT MEDICATIONS AND TREATMENT

Additional concurrent chemotherapy or radiation therapy may not be administered. Sedatives, antibiotics, analgesics, antihistamines, steroids, G-CSF, or other medications as well as red blood cells, platelet or fresh frozen plasma transfusions may be given to assist in the management of pain, infection, and other complications of the malignancy including adverse events.

Data on potential interactions between erlotinib and CYP3A4 inhibitors are lacking. Although caution and careful monitoring are recommended when use of these compounds are necessary, usage does not exclude subjects from participating in this trial (see Appendix D for a list of CYP3A4 inhibitors).

Because of potential for drug-drug interaction between erlotinib and warfarin, subjects in this study who are receiving concomitant warfarin therapy will have INR results obtained at screening and during treatment as follows: weekly for the first 5 weeks and then at each cycle.

13.1 ADVERSE-EVENTS GUIDELINES FOR ALL STUDIES (IND AND NON-IND)

13.2 Assessment of Adverse Event Severity & Relationship to Study

An adverse event temporarily related to participation in the study should be documented whether or not considered to be related to the test article. This definition includes intercurrent illnesses and injuries and exacerbations of preexisting conditions. Include the following in all IND safety reports: Subject identification number and initials; associate investigator's name and name of MTF (Medical Treatment Facilities); subject's date of birth, gender, and ethnicity; test article and dates of administration; signs/symptoms and severity; date of onset; date of resolution or death; relationship to the study drug; action taken; concomitant medication(s) including dose, route, and duration of treatment, and date of last dose.

A serious adverse event is any event that is: fatal; life-threatening (life-threatening is defined as the patient was at immediate risk of death from the adverse event as it occurred); significantly or permanently disabling; a congenital anomaly/birth defect; or requires in-patient hospitalization.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. In addition, laboratory value changes may require reporting.

Reports of all serious adverse events must be communicated to the appropriate Institutional Review Board (IRB) or ethical review committee and/or reported in accordance with local laws and regulations.

13.3 Procedures for Recording Adverse Events

Adverse events will be recorded for all patients from the time of consent until 30 days following the last dose of study treatment (including those withdrawing from the study treatment because of toxicity). All Adverse events that are observed, either during the study period, or prior to the 30th day following the last dose of study drug(s), will be followed until resolution or stabilization.

All Adverse Events regardless of seriousness or relationship to study treatment, including those occurring during the 30 days follow-up period, are to be recorded in the Case Report Form. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the study treatment.

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow the outcome of any **Adverse Events** (clinical signs, clinically significant laboratory values or other, etc.) until resolution or stabilization.

In the case of any **Serious Adverse Event** during the study period, the patient must be followed until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. (For IND studies, the sponsor may request additional investigations if indicated).

13.4 Definition of Serious Adverse Experiences (Events)

The U.S. Code of Federal Regulations, Title 21: Part 312.32, April 1, 1999 defines a serious adverse drug experience as:

“Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.” Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.5 Definition of Unexpected Adverse Drug Experience

Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

13.6 Procedures for Reporting Serious Adverse Events for All Studies (IND and Non-IND)

A written report should be submitted to the Institutional Review Board (IRB) according to the requirements of the assigned IRB for patients enrolled at each site.

Reports of all serious adverse events must be communicated to the appropriate Institutional Review Board (IRB) or ethical review committee and/or reported in accordance with local laws and regulations. Unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study, and all subject deaths related to study participation should be promptly reported by phone (), by email (), or by facsimile () to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-HRPO, ()

Additional guidelines for those studies that are IND studies with M.D. Anderson Cancer Center serving as the sponsor are listed in section 13.6.

Other additional requirements may apply depending on the protocol contract, and requirements of the drug supplier (i.e. Medwatch forms or other reports may be required for submission to the drug supplier, etc.).

13.7 Procedures for Reporting Serious Adverse Events for IND studies (MDACC is the sponsor)

All expected and unexpected events that fall into the definition of an SAE as defined above in the CFR 312.32 must be reported.

All events falling under the definition of serious adverse event that are not listed in the protocol as being expected or anticipated, and occurring within 30 days following the last treatment date, must be reported in a written report to the sponsor within two working days and according to the guidelines that follow.

In addition, each site must report to their assigned IRB of record according to that IRB's guidelines

13.8 Genentech Reporting Requirements

Investigators will submit written reports of all SAEs, regardless of attribution, to Genentech within 48 hours of learning of the events. For initial SAE reports, investigators should record all case details that can be gathered within 48 hours. These should be faxed immediately upon completion to Genentech's Drug Safety Department at:

or

Relevant follow-up information should be submitted to Genentech's Drug Safety as soon as it becomes available and/or upon request.

13.9 Reporting of Subject Death

The death of any subject during the study or within 30 days of study completion (as defined above), regardless of the cause, must be reported within 24 hours by telephone, to the principal investigator and/or study coordinator. If the subject death is determined to be related to study participation, the death should also be reported to the USAMRMC ORP HRPO. A full written report must follow as soon as possible. If an autopsy is performed, the report will be requested if available to be provided to the Sponsor.

Reports of all **serious adverse events, including deaths**, must be communicated to the appropriate Institutional Review Board or ethical review committee and/or reported in accordance with local law and regulations.

13.10 Known Adverse Events Relating to the Underlying Clinical Condition

These will be reported on the chart and in the study case report forms.

13.11 Case Report Form

All adverse events, regardless of severity or causality, will be recorded in a timely manner on the Case Report Form. Adverse event onset and resolution dates, severity/grade, outcome, any action taken due to an AE, and the relationship to the investigational study agent(s) will be documented.

13.12 Notification of Serious Adverse Events

All Grade 3 and 4 toxicities and serious adverse events and deaths, regardless of causality and expectedness, must be reported immediately to the appropriate Institutional Review Board (IRB) or ethical review committee and/or reported in accordance with local laws and regulations.

13.6.1 Adverse Experience Reporting Forms

SAEs will be reported to the sponsor on a template form that will be provided to each site. If needed, a copy of all relevant examinations that have been carried out and the dates on which these examinations were performed should be attached. For laboratory results, normal ranges should be included. Patient name should be marked out and initials and study number included on all attachments.

13.6.2 Reporting to MD Anderson Office of Research Education & Regulatory Management (Sponsor)

In case of a serious adverse event, the following actions must be undertaken by the investigator: (Please note that these are *in addition* to reporting that is required by the local IRB, the USAMRMC ORP HRPO, and in some cases, the drug supplier.)

The SAE must be reported to the sponsor utilizing the sponsor's template "Multicenter Serious Adverse Event Report".

Please e-mail the completed SAE form, and attachments if indicated, to mdaccsafetyreports@mdanderson.org. Reports should be received by the sponsor representative within 2 working days of the research teams' knowledge of the event.

The e-mail must be sent from the PI's e-mail address, or the PI must be copied in the e-mail containing the form. For problems sending the form or other questions, please contact [redacted] Safety Project Manager a [redacted]. As an alternative contact, please call [redacted] manager of ORERM IND Office (sponsor)

Death or life-threatening events that are possibly, probably or definitely related to drug must be reported within 24 hours. The sponsor IND safety coordinator must be notified by phone immediately, in addition to fax or overnight mail as listed above.

13.6.3 External Adverse Experiences / Safety Reports

All external adverse events/safety reports received from the the sponsor (MD Anderson) should be submitted to each sites' assigned IRB by the research personnel at that particular site and according to their local regulations.

13.6.4 Reporting Requirements of Sponsor

The MDACC safety coordinator will process and submit any required safety information to the FDA and other entities as required by CFR312.32 "IND Safety Reports".

13.7 Ligand Reporting Procedures for Serious Adverse Events Related to Bexarotene

If an SAE is considered to be related to bexarotene and is not expected according to bexarotene package insert, then fax copy of SAE report to:

Attention:

Fax: [redacted]

Or

Fax: [redacted]

14.1 STATISTICAL CONSIDERATIONS

14.2 Background

With the advancements in molecular biology and genomic research in the past decade, many target-based agents have been developed for mechanism-based therapy. At the dawn of the era of personalized medicine, we propose to develop innovative clinical trials with state-of-the-art statistical designs by applying adaptive randomization with an underlying hierarchical Bayes model. Our two major goals are to characterize the molecular signature of individual tumors and offer best-fit targeted therapy to patients (Carr et al, 2004) and to identify promising treatment agents for future development. In this application, we propose to apply an outcome-based adaptive randomization design to allocate patients to the best-fit therapies according to estimated probabilities of success. The advantage of such a design is that patients are assigned to the treatments more likely to work with higher probabilities based on cumulative data at hand. Compared with equal randomization, adaptive randomization is more rational and more appealing ethically. (Palmer et al, 2002; Thall et al, 2002)

The idea of adaptive randomization is not new. The simple adaptive randomization design has previously been called “play the winner,” “biased coin,” and “urn,” for example. Review articles of its use in clinical trials can be found in Rosenberger (Rosenberger et al, 1999), Biswas (Biswas, 2001), and Rosenberger and Lachin (Rosenberger et al, 2002). Adaptive randomization has been expanded under the Bayesian framework because it provides a natural way to incorporate prior knowledge. In addition, Bayesian adaptive randomization can include covariate information to better predict patient outcome. (Thall et al, 2005) Unlike the traditional frequentist approach, the Bayesian design allows continuous learning and improvement of the model based on observed, cumulative data. Hence, as the trial progresses, this method not only continues to refine the model of predicting the response to treatment conditional on covariates but also allows the treatment of more patients with more promising regimens based on the covariates and up-to-date data. In addition, the hierarchical Bayes model provides a more efficient way for estimating model parameters by allowing “borrowing strength” across biomarker groups with similar response patterns. Our proposed method integrates the current development of molecular prognostic markers and tailored targeted therapy. (Maione et al, 2004; Vielh et al, 2005)

14.3 Statistical Design

The BATTLE proposal is composed of five clinical trials and the corresponding basic science research components. The umbrella protocol for the clinical trials will obtain patient consent for comprehensive biomarker screening and on the basis of biomarker profiles, assign patients via a Bayesian adaptive randomization scheme into one of the four targeted therapy trials. The goal is to estimate the efficacy of the targeted therapies adjusted by biomarker profiles and, in the meantime, treat patients with the agents most likely to work based on each individual’s biomarker profile.

Biomarker Profile Assessment

In the BATTLE umbrella protocol, all eligible patients will have biopsy samples taken for biomarker profile assessment before randomized allocation. Four types of biomarkers (EGFR, K-ras and/or B-raf, VEGF and/or VEGFR expression, and RXR and/or cyclin D1 expression) will be assessed. Each

patient will be classified into the following five biomarker groups (MGs) based on his or her profile. In addition, each patient will be assigned to one of the four treatment groups. Therefore, there will be a total of 20 subgroups (defined as a combination of MG and treatment group) given five MGs and four treatment groups.

Specific information on the biomarker assessment and the assignment of biomarker groups is listed in the chart below.

Biomarker	Assay	Test Result	Result Summary
EGFR			
EGFR Mutations (exons 18 - 21)	DNA, sequencing	Mutation (Yes/No): Exon:	Positive (Mutation Yes and/or Amplification Yes and/or Polysomy Yes) <input type="checkbox"/>
EGFR Overrepresentation	DNA, FISH	EGFR:Chrom 7 Ratio: Amplification (Yes/No): Polysomy (Yes/No):	Negative <input type="checkbox"/>
K-ras-B-raf			
K-ras Mutations (codons 12, 13, 61)	DNA, sequencing	Mutation (Yes/No): Codon:	Positive (K-ras mutation Yes and/or B-raf mutation Yes) <input type="checkbox"/>
B-raf Mutations (exons 11 and 15)	DNA, sequencing	Mutation (Yes/No): Exon:	Negative <input type="checkbox"/>
Angiogenesis			
VEGF Expression	Protein, IHC	Cytoplasmic Expression Score:	Positive (VEGF score >100 and/or VEGFR-2 score >100) <input type="checkbox"/>
VEGFR-2 Expression	Protein, IHC	Cytoplasmic Expression Score:	Negative <input type="checkbox"/>
RXR/Cyclin D1			
RXR α , β , γ Expression	Protein, IHC	RXR- α Expression Score - Cytoplasm - Nuclei RXR- β Expression Score - Cytoplasm - Membrane RXR- γ Expression Score - Cytoplasm - Nuclei	Positive (Nuclear RXR- α score >30% and/or Cytoplasm RXR α score >200 and/or Cytoplasm or Membrane RXR- β < score >200 and/or Cytoplasm RXR γ score >200 and/or Cyclin D1 IHC score >10% and/or Cyclin D1 Amplification Yes) <input type="checkbox"/>
Cyclin D1 Expression	Protein, IHC	Expression Score - Nuclei	
Cyclin D1 Amplification	DNA, FISH	Cyclin D1: Chrom 11 Ratio: Amplification (Yes/No):	Negative <input type="checkbox"/>

$$MG = \begin{cases} 1 & \text{if EGFR(+), otherwise} \\ 2 & \text{if K - ras(+), and/or B - raf(+), otherwise} \\ 3 & \text{if VEGF(+), and/or VEGFR(+), otherwise} \\ 4 & \text{if RXR(+), and/or cyclin D1(+), otherwise} \\ 5 & \text{All others. Note that MG 5 also includes patients with} \\ & \text{incomplete or missing biomarker information.} \end{cases}$$

Adaptive Randomization under the Hierarchical Bayes Model

Initially, patients will be randomized equally into one of the four treatment arms. Upon randomizing at least 80 patients (i.e. approximately 20 patients per treatment arm), patients will be adaptively randomly assigned into one of the treatment arms on the basis of the estimated disease control rate of each arm DCR of each treatment arm. If the estimated DCR is less than 10%, then 10% will be used in calculating the randomization proportion. Adaptive randomization will be continued until the last patient is enrolled unless the trial is terminated early because no treatment is effective. As indicated in the schema above, Marker Group 5 will include patients with negative biomarker expression for all of the markers listed in Marker Groups 1-4 as well as patients with incomplete or inevaluable biomarker information due to no viable cells or insufficient amount of tissue in the biopsy samples. We recognize that patients with negative biomarker expression may differ from patients with incomplete or inevaluable biomarker information. Hence, at the end of the trials, analyses will be performed both to include and exclude the patients with incomplete or inevaluable biomarker information. Patients randomized to an assigned treatment will not be allowed to re-enter the umbrella trial right away and be re-randomized to another treatment protocol. The example below and Table 4 demonstrate how to adaptively randomize patients with positive EGFR into the four treatment groups:

- Step 1: Prior knowledge of disease control rates is proposed. Suppose the prior DCRs are 0.6, 0.3, 0.2, and 0.05 for treatment arms 1, 2, 3, and 4, respectively. As discussed earlier, for the randomization purpose, the DCR for treatment 4 is adjusted to 0.1.
 - Step 2: The standardized DCR is calculated such that the sum equals to 1. For instance, the standardized DCR for treatment arm 1 is $0.50 = 0.6 / (0.6 + 0.3 + 0.2 + 0.1)$.
 - Step 3: Assume the next patient is randomized to Treatment 1, is treated, and has a response. The posterior DCRs for each of the treatment groups are updated by combining prior DCR and available patient information. For example, the estimated (i.e., model-based) DCR for Treatment 1 becomes 0.7.
 - Step 4: Because the model-based DCR for treatment 4 is 0.05, it is adjusted to 0.1 for randomization purposes only.
 - Step 5: Similarly, the adjusted DCRs are standardized so that the standardized DCRs total 1. For example, the standardized DCR for treatment arm 1 is $0.54 = 0.7 / (0.7 + 0.3 + 0.2 + 0.1)$.
 - Step 6: The next patient with an *EGFR* positive is randomly assigned into the four treatment groups based on the standardized DCRs. In other words, the chances of being assigned into treatments 1, 2, 3, and 4 are 54%, 23%, 15%, and 8%, respectively.
- The trial continues.

Table 4. Disease control rates for the outcome-based adaptive randomization – An illustrative scheme

Treatment Arm	Prior (Step 1)	Adjusted (Step 1)	Standardized (Step 2)	Posterior (Step 3)	Adjusted (Step 4)	Standardized (Step 5)
1	0.6	0.6	0.50	0.7	0.7	0.54
2	0.3	0.3	0.25	0.3	0.3	0.23
3	0.2	0.2	0.17	0.2	0.2	0.15
4	0.05	0.1	0.08	0.05	0.1	0.08

This randomization scheme is proposed because patients with different biomarker status may have different responses to each treatment, and we should take the biomarker status into consideration when assigning patients into treatment arms. For example, if patients with positive EGFR are more likely to respond to erlotinib than the other treatment agents, it will be inappropriate to assign patients into all four treatment arms equally. Therefore, the goal of this randomization scheme is to assign, on the basis of their biomarker status, more patients into the groups where they will be more likely to respond; that is, to ensure every patient receives the treatment most appropriate for him or her with a high probability. It is important to recognize that a probability statement is included because we do not know the outcome of any given treatment with certainty. Therefore, the adaptive randomization allows us to best align patients' biomarker profile with the corresponding promising treatment with high probability.

We choose the 8 week progression-free survival rate as the primary endpoint for the phase II studies. Prior study showed that the median time to progression was 8.5 weeks and the progression-free survival rate at 26 weeks was 17% for patients with advanced NSCLC previously treated with chemotherapy. (Fossella et al, 2000) A "success" or "disease control" to treatment is defined as a patient being progression free at 8 weeks after randomization. The primary objective is to estimate the "success rate" or "disease control rate" for each treatment arm given the covariates.

The Bayesian ordinal probit model (Albert et al, 1993) will be used to characterize the DCR, and the Gibbs sampling approach will be used to approximate the posterior distributions of the parameters. A total of 500 Markov chain Monte Carlo (MCMC) iterations will be generated after 500 burn-in draws, and the MCMC outputs will be sampled at every other iteration. Therefore, a total of 250 MCMC outputs will be used to make posterior inferences. More detailed specification of the model is given below.

Let i , j , and k be the indexes for subject, treatment arm, and biomarker group, respectively. The random variable y_{ijk} is the disease control status for the i^{th} subject in biomarker group k and treatment j . Associated with each y_{ijk} is a latent variable z_{ijk} , which is assumed to be drawn from an independent normal distribution centered at μ_{jk} with a variance of 1. Define $y_{ijk} = 1$ if $z_{ijk} > 0$ and $y_{ijk} = 0$ if $z_{ijk} \leq 0$. The DCR for treatment j and biomarker group k is estimated as the probability of z_{ijk} being greater than 0. That is,

$$y_{ijk} = \begin{cases} 1 & \text{if } z_{ijk} > 0 \\ 0 & \text{otherwise} \end{cases}$$

$$z_{ijk} \sim N(\mu_{jk}, 1), \text{ for } i = 1, \dots, n_{jk}$$

$$\Pr(y_{ijk} = 1) = \Pr(z_{ijk} > 0)$$

The mean of the latent variable z_{ijk} , jk , is assumed to follow a normal distribution centered at Φ_j with variance σ^2 . In addition, for a given treatment group, a hyper-prior centered at 0 with a fixed prior variance is imposed on the location parameters $(\mu_{j1}, \dots, \mu_{j5})$. The detail of the model structure is as the following:

$$\begin{aligned} z_{ijk} &\sim N(\mu_{jk}, 1), \text{ for } i = 1, \dots, n_{jk} \\ \mu_{jk} &\sim N(\Phi_j, \sigma^2), \text{ for } k = 1, \dots, 5 \\ \Phi_j &\sim N(0, 10^6), \text{ for } j = 1, \dots, 4 \end{aligned}$$

This model structure allows borrowing strength across different biomarker groups. The degree of borrowing is determined by the value of the prior variance, σ^2 . The smaller the variance is, the more borrowing is allowed because the location parameters in five biomarker groups within a treatment are more similar. In the simulation studies, we set the prior variance as 10^6 , which results in very little borrowing. The little or no borrowing provides us a conservative estimation of the operating characteristics of the trial because if indeed the responses in different biomarker groups are similar, the correct conclusion can be reached sooner. Smaller variance can be applied and sensitivity analysis by varying the variance can be done to further study the performance of the proposed hierarchical Bayes model. Denote the standard DCR by θ_{jk} and the critical probabilities for the early stopping (i.e., suspension for new patient enrollment) by δ_L . The trial will be terminated for the j^{th} treatment arm and k^{th} biomarker group if $\Pr(\Pr[z_{ijk} > 0 | \text{Data}] > \theta_{jk}) \leq \delta_L$. We choose 0.5 and 0.1 for θ_{jk} and δ_L , respectively, which means that if, given the current data, there is less than a 10% chance that the DCR in this subgroup will be greater than the target DCR, then the treatment will be suspended within this subgroup. Under the Bayesian ordinal probit model described above, the data used in this adaptive decision rule include the data from all biomarker groups combined so that the biomarker groups borrow strength from each other statistically. The stopping rule will be applied after the adaptive randomization begins, which corresponds to approximately 20 patients per treatment group. Let θ_{jk}^* and δ_U be the clinically meaningful target and critical probabilities for declaring an effective treatment, respectively. The treatment will be considered a success if $\Pr(\Pr[z_{ijk} > 0 | \text{Data}] \geq \theta_{jk}^*) > \delta_U$. In this study, we set θ_{jk}^* and δ_U at 0.3 and 0.8, respectively, which means that if, given the current data, a 30% or higher DCR is observed in more than 80% patients, the treatment will be declared a success for this biomarker group. The parameters are derived such that the resulting design has good frequentist properties. The operating characteristics of various scenarios will be evaluated. In this

phase II evaluation with multiple biomarkers, multiple treatment arms, and limited sample size, our target is to achieve a maximum type I (false-positive) error rate of 20% with 80% power. We allow a high type I error rate in order not to miss any potentially effective treatment. After effective treatments are identified, the results will be confirmed by larger studies in the future.

14.4 Statistical Properties of the Design

The statistical properties of the proposed design have been evaluated through simulation studies. We propose to randomize a total of 250 patients with the goal of reaching 200 fully evaluable patients. The “fully evaluable” patients are defined as patients with full biomarker profile assessed and evaluable for the primary endpoint of 8-week disease status. The proportions of patients with different biomarker profiles were estimated based on preliminary data generated by the Biomarker Core. We found that, with 250 patients, the proposed design yielded excellent operating characteristics that met or exceeded the commonly acceptable criteria for designing clinical trials. The proposed design provides accurate estimates for the true DCR in each of the biomarker-treatment arm combination, identifies treatments with high and low probabilities of success, and allocates more patients in the treatment arms more likely to generate a disease control. With early stopping rules, the efficiency of the design is improved further: ineffective treatment arms will be more likely to be closed to new patients. Compared with the conventional approach, it is a “smart” design with many desirable operating characteristics.

Based on our preliminary data, the biomarker groups are defined and their distributions listed in Tables 5 and 6. The operating characteristics and detailed description on the statistical model are given in statistical design manuscript in the Appendix R.

TABLE 5. ASSUMED FREQUENCY DISTRIBUTIONS OF BIOMARKERS

MG	Biomarker				Frequency
	EGFR	K-ras and/or B-raf	VEGF and/or VEGFR	RXR and/or cyclin D1	
1	+	+	+	+	0.00
1	+	+	+	-	0.00
1	+	+	-	+	0.00
1	+	+	-	-	0.00
1	+	-	+	+	0.04
1	+	-	+	-	0.04
1	+	-	-	+	0.04
1	+	-	-	-	0.03
2	-	+	+	+	0.05
2	-	+	+	-	0.05
2	-	+	-	+	0.05
2	-	+	-	-	0.05
3	-	-	+	+	0.15
3	-	-	+	-	0.15
4	-	-	-	+	0.25
5	-	-	-	-	0.10

MG #1 depicts the cases with positive EGFR; in this situation, Erlotinib (treatment arm #1) will be most effective.

MG #2 depicts the cases with positive K-ras and/or B-raf; in this situation, BAY43-9006 (treatment arm #2) will be most effective.

MG #3 depicts the cases with positive VEGF and/or VEGFR expression; in this situation, ZD6474 (treatment arm #3) will be most effective.

MG #4 depicts the cases with positive RXR and/or positive cyclin D1 expression; in this situation, Erlotinib plus Bexarotene (treatment arm #4) will be most effective.

MG #5 depicts the cases with all negative biomarker expressions; in this situation, all four-treatment arms will be equivalently effective.

Table 6 Summarized assumptions of frequency distributions of biomarkers

MG	Biomarker				Frequency
	EGFR	K-ras and/or B-raf	VEGF and/or VEGFR	RXR and/or cyclin D1	
1	+	x	x	X	0.15
2	-	+	x	X	0.20
3	-	-	+	X	0.30
4	-	-	-	+	0.25
5	-	-	-	-	0.10

x, the biomarker can be either positive or negative.

Power and Sample Size Calculations. The sample size is determined using the adaptive randomization design described in the umbrella trial above. The design will have a high probability of providing correct classification with a false-positive rate (type I error) of about 20% assuming a null DCR of 30%. If the target DCR is 50% or 60%, the false-negative rate (type II error) will be 25% and 10%, respectively. The choice of type I and II error rates is attuned to the spirit to common phase II designs. It is assumed that the treatment will have a target DCR of 50%. Consider a single-arm trial in which no disease control is observed for five patients: there will be a 97% chance to rule out the target DCR (Table 7). If the DCR is 20%, 30%, or 40%, the probability of detecting at least one disease control out of five patients is 67%, 83%, and 92%, respectively. The DCR can be estimated with a standard error no larger than 0.22, 0.16, 0.13, 0.11, and 0.09 assuming sample sizes of 5, 10, 15, 20, and 30, respectively. The number of patients in Table 7 shows the possible realization of each of the 20 combinations of the treatment by marker subgroups.

Table 7: Probability of detecting at least one disease control, by disease control rate (DCR) and sample size

No. of patients	Probability of detecting at least one response given				Standard Error
	20% DCR	30% DCR	40% DCR	50% DCR	
5	67%	83%	92%	97%	0.22
10	89%	97%	99%	100%	0.16
15	96%	99%	100%	100%	0.13
20	99%	100%	100%	100%	0.11
30	100%	100%	100%	100%	0.09

14.5 Data Analysis Plan

Upon the completion of the study, data from all randomized patients who receive any one of the four treatment regimens, regardless of the treatment duration, will be included for the toxicity analysis. All randomized and eligible patients who received at least one cycle (4 weeks) of treatment will be included for the efficacy analysis. The percentage of patients who do not complete at least one cycle of the treatment will be documented with the reasons listed. Due to the nature of the phase II study, no intent-to-treat analysis is planned.

After the biomarker profiles for previously treated NSCLC patients are characterized and the patients are stratified into biomarker groups, the biomarker group-specific, 8-week progression-free survival rates of each treatment arm (erlotinib only, ZD6474, bexarotene plus erlotinib, and BAY-42-9006) will be determined. In addition, a "success" or "disease control" to treatment is defined as a patient being progression free at 8 weeks after being randomly allocated into one of the four treatment groups.

Descriptive statistics and exploratory data analysis will be applied for data screening and summary. Categorical variables will be summarized in frequency tables. Continuous variables will be summarized using the mean (\pm s.d.) and median (range). The Pearson correlation or its non-parametric analogue, the Spearman correlation, will be used to assess association among variables. Scatter plots and other plots will be used to characterize associations among variables. The primary endpoint, disease control at 8 weeks, and the disease control rate defined as the percentage of patients without progression at 8 weeks will be estimated for each treatment and each treatment-biomarker combination. Under the Bayesian framework, the inference will be based on the posterior distribution. Both the posterior mean and 95% Bayesian credible interval will be computed. In addition to the prior specified in the Statistical Design section, sensitivity analysis will be performed by varying the prior from non-informative prior to enthusiastic prior and to skeptical prior. The conclusion will be contrasted and compared. Bayes factor will be computed as the Bayesian alternative for hypothesis testing. Standard statistical methods will be applied to analyze continuous, discrete, and survival data. For example, Kaplan-Meier estimates will be constructed for the overall survival and time-to-disease progression. Cox regression will be applied to assess the effect of covariates on time-to-event outcomes. Modulation of biomarkers will be analyzed by the paired-t test, Wilcoxon sign-rank test, mixed model, or the generalized estimation equations method, whenever appropriate. Both Bayesian and frequentist methods will be applied and the results will be compared to derive a robust inference.

The progress of clinical trial conduct and the interim study result will be reported to the M. D. Anderson Data Monitoring Committee (DMC) annually or more frequently if required by the DMC. Any deviation from the data analysis plan will also be reported to DMC for their comments, and then, submitted to HRPO for final approval.

14.6 Data Collection Plan

Study specific Case Report Forms (CRF's) will be created for data collection. Upon identifying the potentially eligible patients, a unique study ID will be generated. The study ID will be used throughout the data collection and reporting process to ensure the patients' anonymity. A study specific (DoD-BATTLE) relational database with a web-based front end will be created to facilitate the study conduct and data collection including registration, randomization, scheduling, and data entry of clinical and laboratory information. Study's research nurses are responsible to fill in CRF's and enter data into the

web-based database through the remote data capturing mechanism from each participating site. The timeline for study visits and procedures that the study subject will participate can be found in section 8.2: Treatment Evaluations. The database has a built-in mechanism for data validity checking and internal consistency checking to improve the data quality. Missing and deficiency reports will be generated automatically. In addition, we plan to audit all the CRF's (100% audit) in the first 10 patients enrolled in each site. Thereafter, at least 10% of the CRF's in the subsequent patients will be randomly selected for audit to ensure the data quality. For reference purpose, a detailed standard operating procedure (SOP) for conducting audit by the M. D. Anderson Data Management Center is listed in Appendix L.

15.1 INVESTIGATOR OBLIGATIONS

15.2 Replacement of Subjects

Participants who withdraw from the study prior to completion of the study treatments for reasons other than serious adverse events, unacceptable toxicity or progressive disease will be defined as dropouts and will be replaced. Replacement participants will be assigned the next sequential number.

15.3 Institutional Review Board

This study must have the approval of a properly constituted Hospital Ethics Committee, Regional Ethics Committee, or other Institutional Review Board (IRB).

The investigator must submit an annual review and final study report to the IRB or Ethics Committee for review and approval. Copies of the annual review and final study report must also be submitted to the USAMRMC ORP HRPO.

15.4 Informed Consent

All study participants must sign and date an informed consent form prior to study participation. The investigator will be responsible for designing the consent form using appropriate National or Regional Guidelines (equivalent to the American Federal Guidelines Federal Register July 27, 1981, or 21 CFR Part 50, or International Committee on Harmonization-Good Clinical Practice).

The informed consent form must be approved by the IRB or Ethics Committee and the USAMRMC ORP HRPO. State and local laws, and/or institutional requirements may require the disclosure of additional information on the informed consent form. For a detailed description of the UTMDACC Research Informed Consent Process please refer to Appendix M.

A copy of the informed consent form will be given to the participant. The investigator will keep each participant's signed informed consent form on file for inspection by a regulatory authority at any time.

The principal investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

15.5 Record Retention

The investigator and other appropriate study staff will be responsible for maintaining all documentation relevant to the study. Such documentation includes:

- Case Report Forms—must be accurate and up-to-date.
- Copies of all Serious AE reporting forms faxed to the USAMRMC, Human Research Protection Office.
- Participant Files—should substantiate the data entered in the CRFs with regard to laboratory data, participant histories, treatment regimens, etc.
- Participant Exclusion Log—should record the reason any participant was screened for the study and found to be ineligible.
- Drug Dispensing Log—should record the total amount of study drug received and returned to sponsor, and the amount distributed and returned or destroyed. This information must agree with the information entered in the CRFs.
- Informed Consent Forms—completed consent forms from each participant must be available and verified for proper documentation.
- Informed Consent Log—must identify all participants who signed an Informed Consent Form so that the participants can be identified by audit.

Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information. The Investigator must keep on file protocols, amendments, IRB approvals, all copies of Form FDA 1572, all correspondence, and any other documents pertaining to the conduct of the study for a minimum of two (2) years after notification by USAMRMC, Human Research Protection Office of either FDA approval or discontinuation of the IND (if applicable).

15.6 Case Report Forms

Data recorded on Case Report Forms (CRFs) must be completed on a timely basis. The investigator must review all final and corrected CRFs.

If a subject's medical record is needed, it will be requested by the Principal Investigator or Co-Principal Investigator. The requesting investigator (i.e., either the PI or co-PI) will assume responsibility for medical record abstraction, which will be performed by an oncology research nurse and the PI or co-PI. The PI and co-PI are medical oncologists.

15.7 Study Monitoring

Study Investigators and appointed research staff will oversee the study conduct to assure satisfactory enrollment rate, data recording, and protocol adherence at MDACC as well as participating sites. The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review.

15.8 Medical Monitoring

The medical monitor will review all serious and unexpected adverse events associated with this protocol and provide an unbiased written report of the event within ten (10) calendar days of the initial report. The medical monitor should be a qualified physician, other than the principal investigator, not associated with the protocol, able to provide medical care for research volunteers for conditions that may arise during the conduct of the study, and who will monitor the volunteers during the conduct of the study. The medical monitor is required to review all serious and unexpected adverse events (per ICH definitions) associated with the protocol and provide an unbiased written report of the initial report. At a minimum the medical monitor should comment on the outcomes of the adverse event (AE) and relationship of the AE to the test article. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to the USAMRMC ORP HRPO..

M.D. Anderson Cancer Center:

The medical monitor for this study will be

[Redacted signature block]

The medical monitor will forward reports to the U.S. Army Research and Material Command, ATTN:

15.9 Termination of Study

The USAMRMC Office of Research Protections (ORP), Human Research Protection Office (HRPO) and M. D. Anderson will retain the right to terminate the study and remove all study materials from the study site at any time. Specific instances that may precipitate such termination are as follows:

- Unsatisfactory participant enrollment with regard to quality or quantity
- Deviation from protocol requirements that may have an effect on the safety or rights of the subject or the integrity of the study, without prior approval from ORP HRPO and M. D. Anderson.

- Inaccurate and/or incomplete data recording on a recurrent basis
- The incidence and/or severity of adverse drug events in this or other studies indicating a potential health hazard caused by the treatment

15.10 Study Amendments

All revisions (protocol amendments, administrative letters, and changes to the informed consent) will be approved by the IRB and USAMRMC ORP HRPO. The Investigator will not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard (s) to study patients. This will be in accordance to the definitions of amendment and requirements detailed in 21CFR.

The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must also be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

15.11 Protocol Deviations and Violations

Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the USAMRMC ORP HRPO as soon as the deviation is identified. For a detailed description of the procedure for submission of protocol deviations and violations refer to Appendix N.

15.12 Ethical and Legal Considerations

This study will undergo full approval in accordance with the human surveillance requirements of each institution. Blood samples will be obtained for the evaluations as described in the protocol. Tissue samples obtained at the time of prior surgeries will be reviewed before participant enrollment to confirm the participant's diagnosis. Measures will be taken to ensure confidentiality of participant information. Tissue samples will be collected prospectively during the trial. Data collected on paper forms will be stored in locked file cabinets with restricted access. Data collected on electronic media will be stored in computer files with restricted password access. All staff members in the study will be informed prior to employment and at regular intervals of the necessity for keeping all data confidential. Computers will not be accessible to the public and will be located in locked offices. Subjects will be assigned a separate study number to protect subject identification. No patient identifiers will be used in any publications of this research. Data will be maintained indefinitely. When the time comes to dispose of the data, all database files will be deleted, patient identifiers will be removed from all paper forms and documents will be shredded.

15.13 Risks/Benefits

15.12.1 Risks

	<p>nausea, vomiting, abdominal pain, headache, Stomatitis, anorexia, alopecia, pruritis, myalgias, bone pain, cough dyspnea, elevated liver enzymes, interstitial lung dz, ocular changes.</p> <p>Warfarin drug interactions Other Drug interactions which may require dosage adjustments (e.g. azole antifungals, barbituates etc).</p> <p>Caution advised in combination with NSAIDS due to risk of GI bleed</p> <p>Containdicated in subjects with hypersensitivity to components/drug or class</p> <p>Unanticipated risks/ Unknown risks</p>	<p>staff. Medical Monitor assigned.</p> <p>Dose of erlotinib may be reduced and/or stopped in the event of toxic side effects</p> <p>Experienced clinical research center with well qualified staff familiar with this patient population.</p> <p>INR results obtained at screening and during treatment for subjects receiving warfarin</p> <p>Included in consent form</p> <p>Reporting and monitoring mechanism in place for SAE/AE or Unanticipated problems</p>
<p>Bronchoscopy with bronchoalveolar lavage, bronchial washings, bronchial brushings, and bronchial biopsies</p>	<p>Pain, irritation, minor sore throat, mild fever, coughing, bleeding, pneumothorax.</p> <p>May cause breathing problems similar to asthma; Bronchitis, Pneumonia</p> <p>Sedatives given during procedure can decrease breathing function and/or level of oxygen in blood.</p> <p>May have allergic</p>	<p>Risks fully addressed in protocol and ICF.</p> <p>Establish adequate pre-procedure bleeding parameters</p> <p>Use of conscious sedation and topical anesthesia to minimize discomfort and cough.</p> <p>Well trained well qualify medical professionals and rescue meds at beside.</p> <p>Pre-sedation assessment to identify particular risk factors</p> <p>Monitoring of level of consciousness, cardiovascular and gas exchange parameters during procedure and recovery.</p>

	<p>reaction to sedatives or anesthetics.</p> <p>Increase risk of bleeding in participants on warfarin. Also in subjects who may be on other anti-coagulants or ASA.</p>	<p>Advise patients of discontinuation of anticoagulants for an adequate period of time prior to the procedure</p>
CT-guided Core Tumor Biopsy	<p>Pain, Discomfort Bleeding and rarely infection.</p> <p>Coughing Collapsed lung (pneumothorax)</p> <p>Sedatives given during procedure can decrease breathing function and/or level of oxygen in blood.</p> <p>May have allergic reaction to sedatives or anesthetics</p> <p>Increase risk of bleeding in participants on warfarin. Also in subjects who may be on other anti-coagulants or ASA.</p>	<p>Risks fully addressed in protocol and ICF.</p> <p>Establish adequate pre-procedure bleeding parameters</p> <p>Use of conscious sedation and topical anesthesia to minimize discomfort and cough.</p> <p>Well trained well qualify medical professionals and rescue meds at beside.</p> <p>Pre-sedation assessment to identify particular risk factors</p> <p>Monitoring of level of consciousness, cardiovascular and gas exchange parameters during procedure and recovery.</p> <p>Advise patients of discontinuation of anticoagulants for an adequate period of time prior to the procedure</p>
Other Core Biopsy methods (i.e. sub-cutaneous, cutaneous, lymph node bx)	<p>Pain, Discomfort Bleeding and rarely infection.</p> <p>May have allergic reaction to sedatives or anesthetics.</p>	<p>Qualified health care provider with experience in biopsy.</p> <p>Local anesthesia to minimize discomfort</p> <p>Establish adequate pre-procedure bleeding parameters</p>
X-rays, and CT or MRI scans	<p>Radiation exposure</p>	<p>These diagnostic tests are medically necessary to monitor the patient; however, however, low risk of radiation exposure as part of participation in the study.</p>
Collection of data	<p>Breach of Patient privacy and</p>	<p>Patient assigned unique code</p>

	confidentiality	Restricted access to research records Investigators trained in Human Subjects Protection Outline plan for disposition of data in the protocol
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15.12.2 Benefits

It is hoped erlotinib in combination with bexarotene will improve response rates, and/or improve survival when compared to other chemotherapy regimens used in this setting.

Participants will not be financially responsible for any study-related tests outside of accepted standard of care follow-up.

15.13 Gender and Minority Inclusion

Women and minorities will be actively recruited to participate in the trial. We expect that the ethnic distribution of the enrolled participants will reflect the local ethnic mixture of each institution's surrounding community.

15.14 Subject Records

USAMRMC ORP HRPO, M.D. Anderson or their representatives may have access to subject records.

15.15 Publication Statement

Data will be reviewed by the collaborating biostatistician prior to publication. USAMRMC ORP HRPO will have 30 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 10-15 days to review all abstracts. Manuscripts will also be submitted to Ligand Pharmaceuticals for review prior to submission.

15.16 Roles and Responsibilities of Key Study Personnel

_____ will serve as the Study Chairman for this protocol at M. D. Anderson Cancer Center. He will assume primary responsibility for the study.

_____ will serve as Study Co-Chairman of this protocol at M. D. Anderson Cancer Center. He will coordinate and supervise all aspects of the clinical trial, and preparation of results for presentations and publication.

_____ will serve as Study Co-Chairman of this protocol at M. D. Anderson Cancer Center. He will coordinate and supervise all aspects of the clinical trial, and preparation of results for presentations and publication.

_____ will be responsible for the adaptive randomization for patient placement into specific biomarker-integrated protocols for the study.

istuba will perform the biomarker profiling of the tumor tissue for the study.

will perform CT-guided core biopsies for patients enrolled at M. D. Anderson Cancer Center.

will perform bronchoscopies for patients enrolled at M. D. Anderson Cancer Center.

will perform CT scans for patients enrolled at M. D. Anderson Cancer Center.

will serve as the study research nurse. She will recruit participants and maintain study records.

OSI-Pharmaceuticals will supply investigational study agent, erlotinib.

Ligand Pharmaceuticals will supply investigational study agent, bexarotene.

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