Title: Phase II Trial of Adjuvant Erlotinib in Patients with Resected, Early Stage, Non-Small Cell Lung Cancer (NSCLC) with Confirmed Mutations in the Epidermal Growth Factor Receptor (EGFR)

NCT00567359

PROTOCOL **07-259**

Version Date: October 2009

A phase II trial of adjuvant erlotinib in patients with resected, early stage non-small cell lung cancer (NSCLC) with confirmed mutations in the epidermal growth factor receptor (EGFR)

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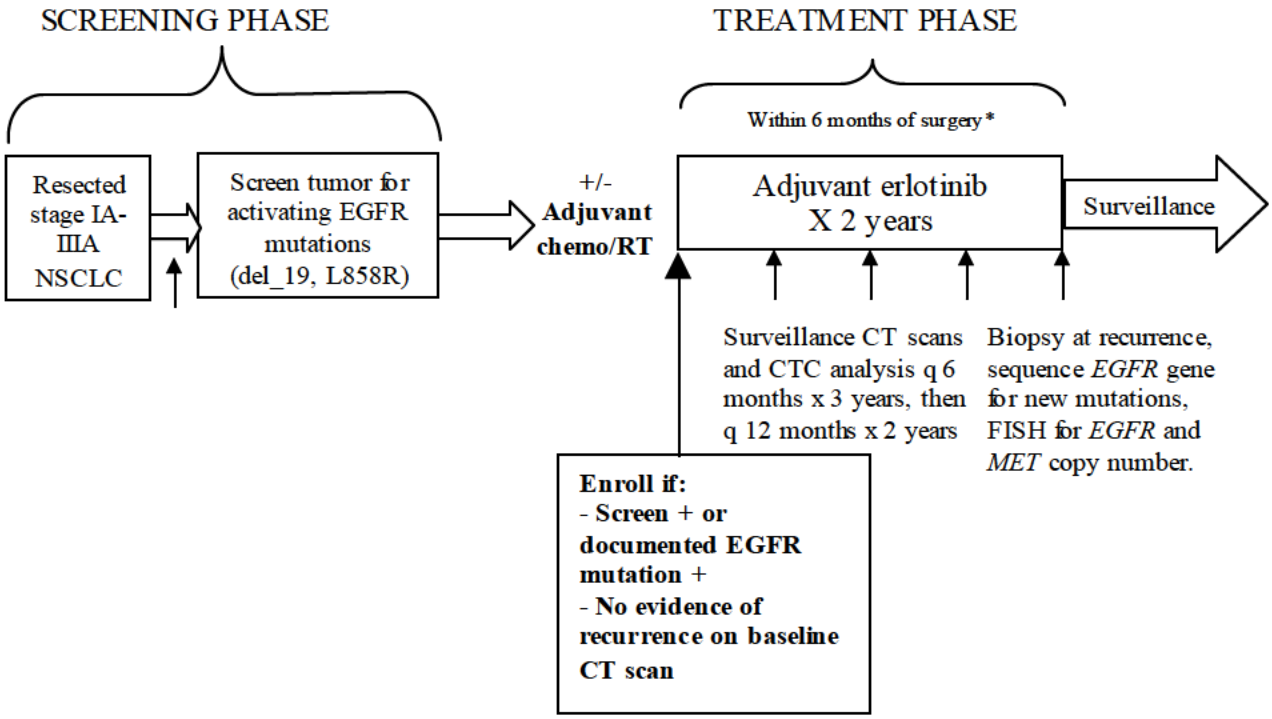
Version Date: October 2009: OSI/Genentech Protocol Reference Number: OSI4308s

Protocol Schema



* If postoperative sequential chemotherapy and radiotherapy, the maximum time between surgery and study registration is 9 months

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INTRODUCTION

1.1 Overview

This Phase II, single-arm, open-label study will investigate the efficacy and safety of adjuvant erlotinib in patients with resected stage I-IIIA non-small cell lung cancer who have confirmed activating mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase domain.

1.2 Background

1.2.1 Adjuvant Chemotherapy for Non-small Cell Lung Cancer

Of the estimated 170,000 patients with non-small cell lung cancer (NSCLC) who will be diagnosed in the United States in 2007[1], only approximately 37% will be potential candidates for surgical resection. Even after resection, many patients will die of distant relapse, with recurrence rates after resection varying from 30% in stage IA to 75% in stage IIIA[2]. This dismal prognosis, even in the setting of early stage disease, speaks to the need for better treatment after surgical resection.

Adjuvant chemotherapy, by definition, is chemotherapy given after surgery to eradicate micrometastatic disease. Adjuvant treatment using platinum-based chemotherapy can increase long-term survival after resection in NSCLC, although the magnitude of benefit is small (4-15%) and seems to be greater in patients with more advanced disease[3-6]. Although patients with resected stage IA and IB disease have relapse rates of 33% and 43% at 5 years[2], there is no evidence that adjuvant chemotherapy improves survival in stage IA disease, and benefit in stage IB remains controversial[7]. Overall, the disease-free survival (DFS) for patients with resected stage I-IIIA NSCLC is approximately 60% at 2 years [3,6,8].

It is clear that current chemotherapy regimens are inadequate, which reflects the inherent insensitivity of NSCLC to chemotherapy. Indeed, platinum doublet regimens such as those used in the adjuvant trials above have only 17-22% objective response rates when used in advanced disease[9]. Quite simply, larger benefits from adjuvant treatment will require more effective treatments. Fortunately, there is a population of NSCLC patients who are highly responsive to treatment, namely those with activating mutations in the epidermal growth factor receptor (EGFR).

1.2.2 Non-Small Cell Lung Cancer and Tyrosine Kinase Inhibitors

Non-small cell lung cancer (NSCLC) is the most common cause of cancer mortality in men and women in the U.S. Chemotherapy and biologically targeted agents can extend survival modestly for patients with locally-advanced or metastatic disease; however, discovery of novel ways to prolong the disease course is a top research priority.

The epidermal growth factor receptor (EGFR; HER1 or ErbB1) belongs to the ErbB family of transmembrane receptor tyrosine kinases (RTKs). Because EGFR is expressed in almost all epithelial cells and tends to be dysregulated and overexpressed in tumor cells, including up to

80% of NSCLC[10], inhibition of the EGFR has been a major area of clinical research in oncology.

One strategy of EGFR inhibition is the use of small molecules such as gefitinib and erlotinib to target the RTK. These molecules compete with ATP for its binding site on the TK, providing reversible inhibition of EGFR RTK signaling[11,12]. In early clinical trials in previously treated, advanced NSCLC patients, gefitinib showed response rates in the 10-18% range[13,14]. It has been clear throughout all studies of gefitinib and erlotinib that subgroups of patients were benefiting from TKI treatment much more substantially than the majority.

Three landmark studies of patients treated with gefitinib and erlotinib demonstrated that most of the patients with significant responses to treatment harbored somatic activating mutations in the *EGFR* gene [15-17]. These mutations are most commonly overlapping deletions in exon 19 or a single point mutation in exon 21 (L858R). They lead to preferential activation of downstream survival pathways and are thought to condition the cell to be reliant upon, or "addicted to" EGFR signaling [18]. This addiction to EGFR signaling confers exquisite sensitivity to signal blockade with TKIs. Since this discovery, the association of *EGFR* mutations with increased response and prolonged survival after TKI treatment has been repeatedly demonstrated. (for review see [19]).

In 2005 the phase III BR-21 trial was published, which showed a survival benefit to erlotinib in the second-line treatment of NSCLC when compared to placebo, but only showed an 8.9% response rate[20]. Post-hoc molecular analysis of a subset of samples from this and other trials of EGFR TKIs indicated that *EGFR* gene copy number and protein expression are also correlated with survival, although these markers appear to be less highly correlated with objective response[21,22]. While the exact role of individual biomarkers to predict clinical benefit from EGFR TKIs is still under investigation, it is clear that the majority of dramatic responses to EGFR TKI therapy are in the patients with *EGFR* mutations, although this does not seem to predict all of the clinical benefit. The relationship of *EGFR* mutation to protein expression and gene copy number is unclear, and little is known about these factors in early stage disease.

1.2.3 EGFR TKIs in the Adjuvant Setting

Several clinical trials have been designed to investigate EGFR TKIs in the adjuvant setting. A randomized phase III trial of adjuvant gefitinib in unselected NSCLC patients was started but closed early after it was recognized that some patients in the advanced setting were developing interstitial lung disease[23], which is now an accepted but rare side-effect of this class of drugs. A second phase III trial, the RADIANT trial, is currently investigating 2 years of adjuvant erlotinib in resected NSCLC patients who have overexpression of EGFR protein by immunohistochemistry or *EGFR* gene copy number by FISH analysis.

The only trial involving adjuvant treatment of EGFR mutant NSCLC was reported in preliminary form at the 2006 ASCO convention[24], in which gefitinib was given for 21 days as induction therapy in 20 patients with light smoking history or tumors having bronchioloalveolar features. The primary endpoint was tumor response as defined as a reduction in bidimensional tumor size of 25%. On biopsy, 7 of these patients had activating EGFR mutations, and all 7 had at least a 10% reduction in bidimensional tumor volume after only 21 days of treatment. Five of

the 7 mutant tumors achieved the primary endpoint of 25% reduction in size, which is consistent with documented response rates in this population, and all patients with mutations and/or a 25% reduction in tumor size preoperatively received adjuvant gefitinib for 2 years afterward. No relapse or survival information is available, but the adjuvant component of this trial is limited by the inclusion of EGFR wild-type tumors and is not designed to detect a survival advantage after treatment with gefitinib.

Finally, the SWOG 0023 trial randomized unselected patients with locally advanced NSCLC to gefitinib versus placebo after definitive chemoradiation[25,26]. This trial, recently updated at the 2007 annual ASCO meeting[26], showed that survival was actually worse in the gefitinib arm, although pneumonitis was no more common in the gefitinib arm than in the placebo arm. While pneumonitis is always a potential risk when taking an EGFR TKI, extensive experience in advanced disease now estimates this risk at 0.7% in the North American population[27]. All anticancer treatments must weigh risk versus potential benefit before proceeding. In unselected patients, who have been shown to have an estimated 9% chance of responding to erlotinib, this risk might seem excessive. This is especially true given the updated results of the SWOG 0023 trial, in which the overall survival in an unselected population seemed to be adversely affected by adjuvant gefitinib. In patients with documented sensitizing mutations in the *EGFR* gene however, where response rates of >75% have been repeatedly described, the risk/benefit ratio swings much farther towards benefit.

1.2.4 Mechanisms of Resistance to EGFR TKIs

Despite the high rate of objective responses to erlotinib and gefitinib in advanced NSCLC patients with activating *EGFR* mutations, most patients eventually will progress while on therapy. One mechanism of resistance is the development of second mutations in the *EGFR* TK domain[28]. The best described mutation is the T790M point mutation, which alters the binding pocket of the ATP binding site such that erlotinib and gefitinib can no longer fit[29]. This mutation has been identified in up to 50% of tumors that relapse after initially responding to EGFR TKIs. Another such mutation is the insertion 20 mutation, which confers *in vitro* resistance to erlotinib and gefitinib, and has been identified in 3 patients who progressed on gefitinib therapy[30].

An additional 20% of patients who relapse after initially responding to EGFR inhibition harbor amplifications of the *MET* tyrosine kinase gene, which allows continued signaling through the PI3 kinase pathway independent of mutant EGFR[31]. Little is known about the remaining 30% of patients who relapse after initially responding, and this area is under active investigation.

1.2.5 Circulating Tumor Cells (CTCs) and the CTC-Chip

The detection of cancer recurrence currently relies on the radiographic detection of new lesions, when tumors already consist of at least 10^9 cells. Recurrent solid tumors are frequently considered incurable, suggesting a need for a more sensitive assay to detect recurrence at the micrometastatic stage when cure might still be possible. In addition, molecular analysis of cancer cells typically requires a tissue biopsy, which carries a degree of risk to the patient. The development of an assay for recurrence using peripheral blood would be tremendously useful in expanding the pool of patients for whom molecular analysis would be possible.

The ability to metastasize is one of the hallmarks of malignancy, and though its mechanisms are not fully described, circulating tumor cell (CTC) distribution through the bloodstream appears to be a vital step in the process.[32,33] Successful capture and characterization of CTCs has tremendous potential as a vehicle to better understand the biology of the metastatic process, and provides an avenue to explore numerous clinical applications via non-invasive, patient-specific genomic analysis. Unlike tumor-derived cells in bone marrow, which can be dormant and long-lived, CTCs have a short half-life (<1 day) and their presence indicates a recent influx from an active proliferating tumor.[34] Hence, CTCs may reflect the clinical status of cancer patients in a dynamic fashion, and could potentially be useful in the early detection of relapse.

At the MGH Cancer Center, we have been developing a device called a "CTC-chip" to capture and quantify CTCs from patient blood samples. Our CTC-chip is a microfluidic platform in which whole blood travels through a forest of micron-sized EpCAM antibody-coated microposts under precisely controlled laminar flow conditions. The arrangement and flow dynamics of the micropost array guides the smaller red blood cells to the periphery of the chip while larger nucleated hematologic and epithelial cells remain in the central portion. CTCs are captured directly onto the sidewalls of the EpCAM antibody-functionalized microposts and remain viable. We have successfully captured an average of 100 viable CTCs per mL of whole blood from 99% of tested advanced NSCLC patients (unpublished observation). The CTC-chip is an ideal tool for studying CTCs in NSCLC patients given its one-step process, the near-universal isolation of large numbers of CTCs from cancer patients, and the ability to capture live cells suitable for molecular analyses. We have preliminary data that suggests that detecting EGFR mutations from CTCs captured via the CTC-chip is feasible and correlates with tumor tissue sample testing.

1.2.6 Pharmacokinetics and Safety of Erlotinib (Tarceva®)

Erlotinib is about 60% absorbed after oral administration and its bioavailability is substantially increased by food to almost 100%. Peak plasma levels occur 4 hours after dosing. Its half-life is about 36 hours and it is cleared predominantly by CYP3A4 metabolism.[35]

The primary toxicities of erlotinib are diarrhea, rash, nausea, headache, mucositis/stomatitis, emesis, and fatigue. A rash occurred in 75% of erlotinib-treated NSCLC patients enrolled in BR.21. Similar incidence of rash have occurred when erlotinib was administered concurrently with chemotherapy including gemcitabine, paclitaxel/carboplatin, and gemcitabine/cisplatin. 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. Other dermatologic manifestations reported in clinical studies or postmarketing use of erlotinib include nail changes, paronychia, painful fissures or cracking of the skin on the hands and feet, and hair growth abnormalities (alopecia, thinning hair, eyelash/eyebrow changes, hirsutism).

The only dose-limiting toxicity is diarrhea, which is dose related and is generally controlled with the addition of loperamide therapy. Grade 3/4 rash and diarrhea occur in 9% and 6% of patients treated with erlotinib, respectively. Rash and diarrhea each result in drug discontinuation in about 1% of patients. Six percent and 1% of patients need dose reductions

for rash and diarrhea, respectively. The median time to onset of rash is 8 days and the median time to onset of diarrhea is 12 days.[35]

There have been infrequent reports of serious interstitial lung disease (ILD), including fatalities, in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumors. In a recent large randomized trial of erlotinib and placebo, the incidence of ILD was the same in both the placebo and erlotinib groups (0.8%).[20] Symptoms can start from 5 days to more than 9 months after initiation of erlotinib. 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, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, alveolitis, and lung infiltration, irrespective of investigator assessed causality. Most cases are associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung cancer, or pulmonary infections. In the event of acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treated instituted as necessary.[35]

The influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of erlotinib is not yet known. However, erlotinib is cleared predominately by the liver, and caution should be used when administering erlotinib to patients with hepatic dysfunction. Erlotinib is also a strong inhibitor of the UDP-glucuronosyltransferase UGT1A1 enzyme responsible for the glucuronidation of bilirubin. Hyperbilirubinemia appears most often to be a side effect related to genetic polymorphisms of UGT1A1. Rare cases of hepatic failure (including fatalities) have been reported during the postmarketing use of erlotinib. Confounding factors for severe hepatic dysfunction have included pre-existing liver disease such as cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs.

Rare cases of myocardial infarction (including fatalities) have been reported during the postmarketing use of erlotinib.

No clinical studies have been conducted in patients with compromised renal function since erlotinib and its metabolites are not significantly excreted by the kidneys.

Rare cases of acute renal failure or renal insufficiency have been reported (including fatalities). Many of these cases have been associated with dehydration associated with nausea, vomiting, diarrhea, and/or anorexia. 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.

Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure of erlotinib (AUC) by 46% and the maximum concentration (C_{max}) by 61%. There was no change to Tmax or half-life. Therefore, drugs that alter the pH of the GI tract may alter the solubility of erlotinib and hence its bioavailability.

The exposure to erlotinib (AUC) increased to a moderate extent, by 39%, and the maximum concentration (C_{max}) by 17%, when erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2.

Erlotinib clearance can be induced by smoking via CYP1A2 induction. Potential drug-drug interaction is expected when erlotinib is taken with CYP1A2 inducers or inhibitors. In a single-dose study in healthy volunteers, the AUC was reduced by 64% in smokers when compared with nonsmokers. In BR.21, current smokers achieved erlotinib trough plasma concentrations that were approximately 2-fold lower than never smokers. Smokers should be advised to stop smoking while taking erlotinib as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking.

Pretreatment or co-administration of erlotinib did not alter the clearance of a prototypical CYP3A4 substrate, midazolam. Therefore, significant metabolic interactions with other CYP3A4 substrates are unlikely. However, the oral bioavailability of midazolam decreased by up to 24% following erlotinib treatment, which was not attributed to a metabolic interaction.

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. In another study, rifampicin pretreatment followed by co-administration of rifampicin with a single 450 mg dose of erlotinib resulted in a mean erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg erlotinib dose in the absence of rifampicin treatment. Therefore, a potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are potent CYP3A4 inhibitors or inducers.

See Appendix 5 for a list of known CYP3A4 inhibitors/inducers. Although caution and careful monitoring are recommended when use of these compounds are necessary, usage does not exclude subjects from participating in this trial, except for EIAEDs, see below.

There is a demonstrated interaction between erlotinib and enzyme-inducing anti-epileptic drugs (EIAEDs), including carbamazipine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone. In a clinical trial of erlotinib in patients with primary brain tumors, EIAEDs reduced exposure to single-agent erlotinib.[36] As a result, patients will not be allowed to take EIAEDs while on this study. See Appendix 5 for a list of EIAEDs.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients while on erlotinib alone and in combination with other chemotherapeutic agents, and concomitant NSAIDS or anti coagulants, including warfarin.

1.3 Study Rationale

This Phase II trial will test the efficacy, safety, and tolerability of 2 years of adjuvant erlotinib in resected, early stage NSCLC patients with confirmed activating mutations in the *EGFR* gene.

As described above, adjuvant chemotherapy for resected NSCLC provides a modest benefit but is not adequate to prevent relapse in a large proportion of patients. The most rational explanation for this failure is the inherent chemoresistance of NSCLC, with only a small percentage of patients (4-15%) deriving benefit from even our most efficacious regimens.

Patients with activating mutations of the *EGFR*, however, represent a unique population of NSCLC patients. In advanced disease, the response rates to EGFR TKIs in this group range from 58%[37] to 75%[38] in prospective trials, and as high as 100%[15,39,40] in retrospective analyses, numbers which are unprecedented in the treatment of NSCLC. If we extrapolate that 75% of patients with micrometastatic disease would have a similar benefit, we can hypothesize that adjuvant erlotinib could delay relapse or even potentially cure the majority of patients with resectable cancer who would otherwise relapse with adjuvant chemotherapy alone.

This trial will provide a complement to the industry-initiated RADIANT trial, as lung cancers with *EGFR* mutations and lung cancers with EGFR protein overexpression and/or increased gene copy number may represent different populations of patients who may derive different levels of benefit from erlotinib treatment. Using biopsies at the time of disease recurrence, this trial will also allow us to collect *EGFR*-mutant NSCLC samples before and after treatment with erlotinib. These samples will provide invaluable information about the mechanisms of de novo and acquired resistance to EGFR TKIs, as well as allowing us to investigate the associations between *EGFR* mutations, protein expression, and gene copy number in primary and recurrent tumors.

2.0 OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is to determine the 2-year disease-free survival of patients with resected, early stage NSCLC who have activating mutations in the *EGFR* gene, after treatment with adjuvant erlotinib.

2.2 Secondary Objectives

The secondary objectives of this study are:

1) To determine the safety and tolerability of 2 years of adjuvant erlotinib.
2) To determine disease free survival in this patient sample.
3) To determine overall survival in this patient sample.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

1) To determine the relationship of *EGFR* mutation status to *EGFR* gene amplification and EGFR protein expression in early stage NSCLC.
2) To determine the relationship of *EGFR* mutation status to *EGFR* gene amplification and EGFR protein expression in recurrent NSCLC.
3) To identify secondary mutations responsible for resistance to erlotinib in recurrent NSCLC.
4) To identify the frequency of *MET* amplification in recurrent, EGFR-mutant NSCLC.
5) To study the ability to detect circulating tumor cells (CTCs) in patients with resected early stage NSCLC, to determine the relationship between CTC quantity over time to disease recurrence, and to identify the relationship between *EGFR* mutation status in CTCs and the primary and/or recurrent tumors.

3.0 ELIGIBILITY

3.1 Study Overview

This is a Phase II, single-arm, open-label study designed to investigate the efficacy and safety of adjuvant erlotinib in patients with resected stage I-III non-small cell lung cancer who have confirmed activating mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase domain.

3.2 Inclusion Criteria

Patients may be enrolled only if they meet all of the following criteria:

1) Pathologically confirmed diagnosis of non-small cell lung cancer of adenocarcinoma histology, including non-mucinous bronchioloalveolar carcinoma and mixed cell types such as adenocarcinoma with bronchioloalveolar features and adenosquamous carcinoma.
2) Stage IA-B, IIA-B, or IIIA by the American Joint Committee on Cancer (AJCC) Seventh Edition staging criteria, see Appendix 1.
3) Patients must have undergone surgical resection with curative intent within 6 months of enrollment.
4) Age equal to or greater than 18 years.
5) Tumor samples must have either exon 19 deletion mutations or the exon 21 L858R point mutation. Other rare EGFR mutations may be eligible after discussion with the overall principal investigator. Mutations detected at outside laboratories will be acceptable for enrollment.
6) Performance status of 0, 1, or 2 on the Eastern Cooperative Oncology Group (ECOG) Performance Status scale, see Appendix 2.

7) Neoadjuvant or adjuvant chemotherapy, radiation, and/or chemoradiation will be allowed as long as no more than 6 months have passed between surgical resection and enrollment. If patients receive sequential chemotherapy and radiation, they are allowed 9 months between surgical resection and enrollment. At least 3 weeks (≥21 days) must have passed since the completion of adjuvant chemotherapy.
8) Adequate organ function including the following
    - Adequate bone marrow reserve:
        - Total white blood cell count (WBC) ≥ 3.0 x 10^9/L
        - Platelet count ≥100 x 10^9/L
        - Hemoglobin ≥9 g/dL
    - Hepatic:
        - Bilirubin: ≤ 1.25 times the upper limit of normal (ULN)
        - Alanine transaminase (ALT): ≤ 2.5 times the ULN
        - Aspartate transaminase (AST): ≤ 2.5 times the ULN
    - Renal: Serum creatinine ≤ 1.5 times the ULN, or creatinine clearance ≥60mL/minute as calculated by the standard Cockcroft-Gault formula, see Appendix 3.
9) Willingness to comply with protocol procedures.
10) Willingness to participate in clinical research as evidenced by their signature on the informed consent form.

3.3 Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be eligible to enter in the study:

1) Radiographic evidence of recurrent NSCLC prior to erlotinib treatment.
2) Confirmed T790M resistance mutation in the primary tumor sample.
3) Prior exposure to EGFR tyrosine kinase inhibitors.
4) Known hypersensitivity to erlotinib, gefitinib, or any closely related drug.
5) Pregnant or breastfeeding. The effects of erlotinib on a fetus are unknown. For these reasons, female subjects of childbearing age must practice acceptable methods of birth control to avoid pregnancy. Male subjects must also practice acceptable methods of birth control to prevent pregnancy of a partner.
6) Any evidence of clinically active interstitial lung disease. Note that patients with chronic, stable radiographic changes who are asymptomatic need not be excluded.
7) Malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.

8) Current use of enzyme-inducing anti-epileptic drugs (EIAEDs), including carbamazipine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone.

9) Evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the study, in the opinion of the investigator.

10) Use of any non-FDA approved or investigational agent within 2 weeks of enrolling onto the trial, or failure to recover from the side effects of any of these agents.

3.4 Subject Registration

A subject may be entered in the study once informed consent has been obtained and it has been determined that the patient meets all eligibility criteria. Following completion of eligibility testing, the research nurse, data manager and the study investigator will confirm patient eligibility. If questions regarding eligibility arise, the overall study chairperson, Dr. Lecia Sequist, will make the final decision regarding approval for registration. Any formal changes to the eligibility criteria must be approved by the institutional IRB. Eligible subjects must be registered through the DFCI Quality Assurance Office for Clinical Trials (QACT) by phone (617-632-3761) or fax (617-632-2295). Patients must be registered prior to the initiation of treatment. The QACT will ask for the following information:

1. Protocol name and number
2. Date the study treatment is scheduled to begin
3. Patient name, address, and date of birth
4. Patient ID number
5. Primary physician
6. Primary treatment institution
7. Confirmation of eligibility (completed QACT checklist, which will be provided to each site at time of initiation)
8. Copy of signed consent form

[redacted]

Please refer to appendix 7, section 5.7

4.0 STUDY TREATMENT

4.1 Overview

This is a Phase II single-arm open-label study of adjuvant erlotinib in patients with resected early stage NSCLC with confirmed activating mutations in the *EGFR* gene.

Within 6 months of surgical resection, patients with clinical characteristics suggesting a high probability of *EGFR* mutation will have their primary tumors screened for activating *EGFR* mutations (i.e. exon 19 deletions, L858R point mutation). Patient with confirmed mutations will be treated with daily oral erlotinib for a maximum of 2 years.

4.2 Treatment Administration: Single agent Erlotinib

4.2.1 Treatment Agent

Substance:	Erlotinib Hydrochloride
Pharmaceutical Form:	Tablets
Source:	Genentech, San Francisco, CA
Procurement:	Medication to be provided by OSI
Unit strength:	150 mg tablets
Daily dose:	See Section 4.2.2
Duration of Use:	Continuous daily dosing starting on Day 1 and continuing for 2 years or until criteria for discontinuation are met, see Section 4.4
Route of Administration:	Oral (swallowed)
Frequency:	Once daily, on an empty stomach

4.2.2 Dosage and Administration Schedule

All patients will begin oral dosing of Erlotinib at 150 mg daily on day 1 of treatment and continue daily dosing without interruption. Patients should take their assigned daily dose at approximately the same time each day. Erlotinib should be taken on an empty stomach, 1 hour before a meal or 2 hours after a meal. Patients will continue with daily treatment for a maximum of 2 years.

4.2.2.1 Missed and Vomited Doses

If a patient inadvertently does not take the Erlotinib dose at their usual time, he or she may take their daily doses anytime as long as it is at least 12 hours before the next dose is due to be taken. Erlotinib should be taken on an empty stomach. The daily treatment schedule will be resumed the next day with the patient taking the scheduled dose at the usual time. If an entire daily dose is skipped, the patient should resume treatment the following day with their regular dose. No "make-up dose" or increased dosing should occur. Patients should report all missed or delayed doses to the study staff.

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. Patients should report all vomited doses to the study staff.

4.2.3 Dose Delays

If a treatment-related toxicity of grade 3 or higher occurs, erlotinib should be held until the toxicity resolves to ≤ grade 1 or pre-treatment baseline. Subsequent treatment should be dose-reduced one dose level as per Section 4.2.4. The investigator also has the discretion to hold erlotinib treatment for any other toxicity, but in this case dose reduction is not required. Treatment may be held for up to 28 days. If the toxicity is not improved to ≤ grade 1 or pre-treatment baseline within the 28-day period, the subject must be withdrawn from the study.

4.2.4 Dose Modification Guidelines

If a treatment-related toxicity of grade 3 or greater occurs, erlotinib should be held until the toxicity resolves to ≤ grade 1 or pre-treatment baseline, and then erlotinib should be dose-reduced one level. Dose reduction levels for erlotinib are 100 mg and 50 mg. The investigator also has the discretion to reduce the dose of erlotinib treatment by one dose level for any other toxicity, in consultation with the principal investigator.

Note that no patient may undergo more than 2 dose reductions. If a third dose reduction becomes necessary, the subject must be withdrawn from the study.

4.3 Concomitant Therapy

Information about concomitant medications will be collected as part of this study during screening, at each evaluation visit, and at the time of study discontinuation, see Section 6.0. Patients are allowed to receive full supportive care therapies concomitantly during the study. No other chemotherapy, immunotherapy, hormonal cancer therapy, radiation therapy, surgery for cancer, or experimental medications will be permitted while the patients are receiving study therapy.

Data on potential interactions between erlotinib and CYP3A4 inhibitors/inducers 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 in general. See Appendix 5 for a list of known CYP3A4 inhibitors/inducers. However, there is a demonstrated interaction between erlotinib and enzyme-inducing anti-epileptic drugs (EIAEDs), including carbamazipine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone. In a clinical trial of erlotinib in patients with primary brain tumors, EIAEDs reduced exposure to single-agent erlotinib.[36] As a result, patients will not be allowed to take EIAEDs while on this study. See Appendix 5 for a list of EIAEDs.

Because of the potential for drug-drug interaction between erlotinib and warfarin, patients in this study who are receiving concomitant warfarin or coumarin derived anticoagulants, should have close monitoring of their INR and prothrombin time and adjustment of the anticoagulant dose as clinically indicated.

4.3.1 Recommendations for Supportive Treatment

The following are recommendations for supportive treatment of expected side effects

Rash: Management of Grade 1 or 2 erlotinib-associated acneiform rash should include continuation of erlotinib and symptomatic management such as moisturizing, analgesics for pain and oral antihistamines for pruritis, see Table 1. The following agents may be used to treat rash: diphenhydramine, topical or oral corticosteroids, and topical (clindamycin) or oral antibiotics (tetracycline, minocycline, doxycycline). Topical drying agents are not recommended. High-potency topical corticosteroids (class I and II) may be effective if used early in therapy. The use of topical immunomodulatory agents, such as pimecrolimus (Elidel) and tacrolimus (Protopic), can also be attempted.[35] Secondary infections of the rash can be treated with oral antibiotics. Systemic steroids are discouraged as treatment for skin toxicity due to lack of efficacy and potential worsening of the acneiform skin rash. If skin rash persists or worsens, dose reduction to 100 mg per day and/or treatment interruption of 5-14 days should be considered. If the dose of erlotinib is reduced for rash, subjects should be maintained at the reduced dose without attempt at dose re-escalation. If rash does not decrease to ≤ grade 1 within 28 days of treatment interruption, then erlotinib should be discontinued and the patient should be withdrawn from the study. Subjects experiencing grade 4 rash should be considered for withdrawal from the study for excessive toxicity.

Diarrhea: For Grade 1 or 2 diarrhea, early intervention should include initiation of anti-diarrheal therapy as described in Table 1. For patients on erlotinib experiencing persistent grade 2 diarrhea despite optimal medical management, consideration of dose reduction of erlotinib to 100 mg per day should be considered as outlined in Section 4.2.4. Management of ≥ grade 3 diarrhea should include holding erlotinib until the toxicity resolves to ≤ grade 1 or pre-treatment baseline. Subsequent treatment should be dose-reduced one dose level. Subjects should be maintained at the reduced dose without attempt at dose re-escalation. If diarrhea does not resolve to ≤ grade 1 within 28 days of treatment interruption then the patient should be withdrawn from the study. Subjects experiencing grade 4 diarrhea should be considered for withdrawal from the study for excessive toxicity.

ILD: Although quite rare, 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 1. Recommended Guidelines for Management Selected 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		
Grade 1 and 2 Tolerable rash	None	Any of the following: oral antibiotics (tetracycline, minocycline[a], doxycycline), topical clindamycin, diphenhydramine, topical or oral corticosteroids at discretion of investigator
Grade 3 Intolerable rash	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.

4.4 Discontinuation of Study Treatment

Patients enrolled on the study will be treated continuously for a maximum of 2 years. Patients will be discontinued from study treatment under the following conditions:

1) The patient has completed 2 years of treatment.
2) Evidence of recurrent disease on surveillance radiographs. When possible and medically appropriate, tissue biopsies should be obtained to prove recurrence.
3) Retreatment criteria are not met within the specified time frame, see Sections 4.2.3.
4) Study therapy exhibits unacceptable toxicity.
5) Investigator or patient requests withdrawal.
6) Severe non-compliance to protocol.
7) Death.
8) Patient lost to follow-up.

4.5 Study Medication Accountability

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs and OSI should be provided with documentation when this has occurred.

Patients who discontinue study treatment will undergo follow-up procedures as described in Sections 5.0 and 6.0.

5.0 STUDY ASSESSMENTS

5.1 Safety Assessments

5.1.1 Overview of Safety Assessments

A secondary objective of this study is to identify the safety and tolerability of 2 years of adjuvant erlotinib. Safety measurements that will be used in the study include physical examinations and clinical laboratory tests (hematology, blood chemistries, creatinine and liver function tests). Patients will be rated for toxicity using the NCI CTC version 3.0, see Appendix 4. Standard toxicity assessment will occur in the screening phase, monthly for the first 6 months of treatment, and then every 3 months until treatment is discontinued. For a table of the required data, see Section 6.0.

Treating investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Institutional Review Board (IRB) to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. All patients experiencing an adverse event that is serious or that caused the patient to discontinue

before completing the study must be followed through an appropriate health care option, until the event resolves or is explained.

5.1.2 History and Physical Examination

The relevant interval history should be obtained during screening, at monthly intervals for the first 3 months (months 4 and 5 are optional and at the discretion of the treating MD) and then every 3 months until treatment is discontinued, at months 30, 36, 48, 60 after 2 years of treatment have been completed, and at the time of study discontinuation. Interval history should include elicitation of interim illnesses and adverse events.

A problem-focused physical examination (PE) will be performed during screening, monthly for 3 months (months 4 and 5 are optional and at the discretion of the treating MD) and then every 3 months until treatment discontinuation, at months 30, 36, 48, 60 after 2 years of treatment have been completed, and at the time of study discontinuation. Every PE should include measurement of body weight, vital signs, and evaluation of the ECOG performance score, see Appendix 2. Measurement of height need only occur at the screening PE. Visit windows after screening/baseline for months 1-3 is +/- 7 days. Starting month 4, the window is extended to +/- 14 days

5.1.3 Laboratory Examinations

Laboratory examinations to be performed during screening for the treatment phase include hemoglobin, white blood cell count including neutrophil count (sum of polysegmented granulocytes and band forms), platelets, bilirubin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, calcium, electrolytes (sodium, potassium), and a pregnancy test (urine or plasma for women of child-bearing age).

Laboratory examinations to be performed at the initiation of treatment, monthly for 6 months and then every 3 months until treatment discontinuation, at months 30, 36, 48, 60 after 2 years of treatment have been completed, and at the time of study discontinuation include hemoglobin, white blood cell count including neutrophil count (sum of polysegmented granulocytes and band forms), platelets, bilirubin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, calcium and electrolytes (sodium, potassium). If screening blood tests were performed within 7 days of starting treatment they do not need to be repeated on day 1.

5.1.4 Adverse Events

An Adverse Event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with NSCLC that were not present prior to the AE reporting period

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period
- Diagnoses and/or symptoms associated with NSCLC should be reported as AEs if they worsen or change in character. Clinical progression of NSCLC should not be reported as an AE.

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinical visit?"

"Have you had any new or changed health problems since you were last here?"

All AEs should be documented, whether or not the AE is considered serious. A description of the event, including its date of onset and resolution, any action taken, and outcome should be provided along with the investigator's assessment of causality. An event that is due to unequivocal progression of disease should not be reported as an AE.

5.1.5 Serious Adverse Events

An event that fulfills at least one of the following criteria will be designated a serious adverse event (SAE). Study site personnel must immediately report SAEs to the IRB, no later than the end of the next business day after becoming aware of the event.

- Results in death
- Requires or prolongs hospitalization (i.e. the AE required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Is immediately life-threatening
- Results in severe or permanent disability or incapacity
- Is a congenital abnormality or birth defect
- Is considered a significant medical event by the investigator based on medical judgement.
- Does not meet any of the above serious criteria but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All SAEs will be recorded once the patient has entered in the study, even if study drug has not yet been administered. After discontinuation from treatment, subjects must be followed for SAEs for 30 calendar days after the last dose of study drug. SAEs occurring more than 30 days after the last dose of study drug(s) will not be reported unless the investigator feels that the event may have been caused by the study drug(s) or a protocol procedure. Any events that are unequivocally due to progression of disease should not be reported as a SAEs.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE. To assess severity of an adverse event, please refer to the NCI CTC version 3.0 (Appendix 4) and Appendix 6.

The causality of SAEs (relationship to the study drug) must be considered by the investigator by answering the question, **"Do you consider that there is a reasonable possibility that the event may have been caused by the drug?"** See Appendix 6 for more guidance on this issue.

All SAEs should be reported and submitted per institutional guidelines. The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are recorded on the CRF and reported to the Sponsor in accordance with protocol instructions.

5.1.6 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be recorded in the patient's medical record and on the appropriate AE or SAE clinical report form page.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity (see Table 2), regulatory seriousness criteria if applicable, suspected relationship to the investigational product (see following guidance), and actions taken.

While most hospitalizations require reporting of an SAE, some events do not require reporting. Examples would be:

- Elective or previously scheduled surgery
- Procedures for pre-existing conditions that have not worsened after the initiation of treatment
- Pre-specified study hospitalizations for observation

Table 2

Adverse Event Grading (Severity) Scale

Grade	*Severity*	*Alternate Description* [a]
1	*Mild (apply event-specific NCI-CTCAE grading criteria)*	*Transient or mild discomfort (< 48 hours); no interference with the patient's daily activities; no medical intervention/therapy required*
2	*Moderate (apply event-specific NCI-CTCAE grading criteria)*	*Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required*
3	*Severe (apply event-specific NCI-CTCAE grading criteria)*	*Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible*
4	*Very severe, life threatening, or disabling (apply event-specific NCI-CTCAE grading criteria)*	*Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable*
5	*Death related to AE*	

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 5.1.7).

[a] *Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI-CTCAE listing.*

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- **YES**

There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge.

- **NO**

Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug).

5.1.7 Reporting of Adverse Events

Please see the Data Safety Monitoring Plan (Appendix 7) for full details and procedures.

15-Day "Alert Report"

The Sponsor-Investigator is required to notify the FDA of any fatal or life threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of Erlotinib. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be submitted to the FDA via MedWatch to the fax number listed on the form. Please refer to protocol OSI4308s when preparing all reports.

All 15 Day "Alert Reports" that are submitted to the FDA must also be faxed to Genentech Drug Safety and the Lead Coordinating Site:

Genentech Drug Safety: [redacted]

Lecia V. Sequist, MD MPH: [redacted]

5.1.8 Type and Duration of Follow-up of Patients after Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to their resolutions, or until the investigator assesses them as stable, or the patient is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the appropriate AE or SAE CRF page and in the patient's medical record to facilitate source data verification.

For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.2 Efficacy Assessments

5.2.1 Timing and Method of Efficacy Evaluation

Baseline restaging scans will be performed within 28 days of starting study drug. Spiral computed tomography (CT) scans are the preferred method of surveillance.

In order to detect disease recurrences, follow-up CT scans of the chest, abdomen, and pelvis will be performed every 6 months for the first 3 years, and then every 12 months for the next 2 years, according to standard practice. Scans will also be performed if clinically indicated during the interim evaluations. Disease recurrence will be defined as either radiographic or biopsy-

proven evidence of local or distant lung cancer recurrence. In the case of radiographic evidence of recurrence, tissue biopsies should be obtained to prove recurrent disease, unless it is deemed medically unsafe to obtain the biopsy.

5.3 Assessments at the Time of Study Discontinuation

All patients should be evaluated at the time of withdrawal from the protocol. The following evaluations should occur at that visit:

- Relevant interval history and focused physical exam, as per Section 5.1.2
- Laboratory evaluations, as per Section 5.1.3
- If death has occurred, documentation of date of death.

The timing of further follow-up visits will vary for individual patients, depending on their disease status and the presence of ongoing toxicity. After discontinuation from the study for any reason, where possible the patient, patient's family, or the patient's current physician must be contacted every 12 weeks for the following information:

- Survival information until death
- All subsequent chemotherapy, radiation, surgical or other anti-cancer therapies until death.

In addition, any patient who discontinued study treatment for reasons other than objective disease recurrence should continue to have routine surveillance assessments for tumor recurrence according to standard practice in order to collect information on progression of disease.

Where possible, post-treatment biopsy tissue should be obtained for analysis of EGFR status (see Section 5.4).

5.4 Molecular Assessments

5.4.1 *EGFR* mutation testing and FISH analysis

As part of this study, specimens collected initially and at re-biopsy will be further analyzed for EGFR gene copy number, EGFR immunohistochemical staining, and MET amplification. Re-biopsy specimens will also undergo repeat EGFR mutation analysis. Therefore, all sites are strongly encouraged to send available tissue blocks and/or 5 unstained slides for analysis to:

[redacted]

Sites may be directly contacted directly to request these specimens. Results of these tests will be provided to back to sites upon request.

Available unstained sections of paraffin-embedded tumor from patients will undergo microdissection, after which genomic DNA will be extracted. Tumor DNA will be directly sequenced to look for EGFR mutations, including EGFR exons 18-21, using standard procedures. As noted, L858R and exon 19 deletion EGFR mutations detected at other centers or using other methods will also be acceptable. Mutation analysis will be also be performed, whenever possible, on biopsy tissue taken at the time of recurrence to look for changes in the mutation profile of recurrent tumors.

Tumor sections will also undergo fluorescence in-situ hybridization (FISH) analysis using standard procedures and employing fluorescent probes for the *EGFR* locus on chromosome 7p and for chromosome 7q as a reference. A ratio of 7p:7q of > 2.0 will be considered *EGFR* locus amplification. The distribution of *EGFR* copy number in the cellular population will be used to assess for polysomy, using the standard criteria described previously.[41] Samples of tumor taken at the time of disease recurrence will additionally undergo FISH testing to detect amplification of *MET*[31]. Dr. A. John Iafrate will collaborate on the molecular analyses.

Tumor sections will also be stained for EGFR protein expression using immunohistochemistry with commercially available antibodies against human EGFR.

5.4.2 Circulating Tumor Cells (CTCs)

CTCs will be measured in freshly obtained peripheral blood using the CTC-Chip (as described in the background section) at baseline and every 6 months at the same time as the scheduled surveillance scans. CTC analysis will be restricted to the patients enrolled at the MGH and DFCI sites as the blood needs to be tested rapidly and cannot currently be done at outside institutions. The association of CTCs with radiographic disease recurrence will be assessed. *EGFR* mutation testing will be performed on isolated CTCs to determine the relationship between mutation status in the CTCs and that of the primary and/or recurrent tumor samples.

6.0 REQUIRED DATA

Table 3. Standard Required Data

Study plan	**Screen** [b]	**Treatment Period (months)** Months 1-3 visits +/- 7 days [(i)] Months 4-beyond, +/- 14 days											**Follow-up (months +/- 2 weeks)**			**Off-Study** [a]	**Survival Follow-up**
Time	**Day –14**[b]	**Day 1**	**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**Annual x 2**		
Informed consent and confirmation of eligibility	X																
Demography/ Medical History	X																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination and interval history. (including selected adverse events)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory examinations[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Radiological evaluation[d]	X					X		X		X		X	X	X	X		X
CTC assay[e]	X					X		X		X		X		X	X		X
Urinalysis	X	As clinically indicated															
EGFR testing[f]	X[f]	If patient recurs and fresh biopsy material available for testing															
Pregnancy test (if appropriate Urine or plasma)	X	As clinically indicated															
Survival and subsequent therapy[g]																	X[g]

a **Off-Study visit** –The off-study assessments will be performed when the subject meets criteria for study discontinuation, see Section 4.4.

b **Screening** – Screening can occur anytime in the patient's treatment such that treatment with erlotinib begins within 6 months of surgical resection.

c **Laboratory Studies** – screening studies include CBC, LFTs, BUN, Cr. Studies at the start of each cycle of treatment include CBC, LFTs, BUN, Cr, calcium and electrolytes. If screening labs done ≤ 7 days of study start, they do not need to be repeated on Day 1

d **Radiological evaluation** – CT scans of the chest, abdomen, and pelvis will be performed at baseline, every 6 months for the first 36 months, and then annually until 60 months to check for recurrent disease.

e **CTC** – Circulating tumor cell assay on peripheral blood will be performed at baseline, every six months for 3 years, and then annually until 60 months at the time of radiographic evaluations. Only done at MGH and DFCI.

f **EGFR testing** - EGFR sequencing, FISH for *EGFR* and *MET* gene copy number, and immunohistochemistry for EGFR protein expression. Testing for the initial screening can take place anywhere in the patient's treatment as long as adjuvant erlotinib can start within 6 months of surgery.

g **Survival follow-up** - After discontinuation from the study for any reason, where possible the patient, patient's family, or the patient's current physician must be contacted every 12 weeks for survival information until death. All subsequent chemotherapy, radiation, surgical or other anti-cancer therapies are to be collected until death. A statement of death form should be submitted at any point during the study when a patient has died. *In addition, any patient who discontinued study treatment for reasons other than objective disease recurrence should continue, where possible, to have objective tumor surveillance scans per routine practice guidelines.*

h Selected adverse events will be captured. Please see Appendix 4 for complete list of events and codes

i Months 4 and 5 are optional and at the discretion of the investigator

7.0 STATISTICAL PLAN

7.1 Overview

This is a Phase II single-arm open-label study of adjuvant erlotinib in patients with resected, early stage NSCLC who have activating mutations in the *EGFR* gene. The primary objective of this study is to determine the 2-year disease free survival (DFS) rate in this population. Secondary objectives are to determine the overall safety and tolerability of 2 years of adjuvant erlotinib, as well as to determine the disease-free survival and overall survival in this population.

7.2 Sample Size

This trial will enroll a total of 100 patients.

Based on data from a large single institution experience of early stage resected NSCLC cases known to harbor *EGFR* mutations and treated with adjuvant erlotinib or gefitinib, we would expect the 2-year DFS to be approximately 76% at baseline across all stages as reported for a group of 114 patients.[42] When a similar group of patients at the same institution were treated with adjuvant erlotinib or gefitinib, their 2-year DFS increased to 88%, which gives us an idea of the expected magnitude of benefit.

With 100 patients, the study will have 90% power to observe an improvement in DFS at 2 years from a historical control of 76%, to 86% for patients treated on our study with adjuvant erlotinib, using the one-sided binomial proportion hypothesis test with significance level of 0.1. This degree of improvement is reasonable to expect since metastatic NSCLC patients with *EGFR* mutations have a response rate to erlotinib of about 75% and their progression-free survival on upfront erlotinib is about 9 months, as opposed to the 3 months typically observed with combination chemotherapy.[37, 38, 40] The trial will be deemed successful if at least 82 patients are alive and progression free by 2 years.

7.3 Data to Be Analyzed

All enrolled patients treated with at least one dose of study drug will be included in the safety and efficacy analyses on an intention to treat basis. All enrolled patients treated with at least one dose of study drug and with sufficient and appropriate tumor samples for molecular analysis will be included in the correlative science analyses.

7.4 Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- A definition of patient enrollment
- A summary of data regarding patient discontinuation of study treatment
- A summary of data regarding patient inclusion and exclusion in efficacy and safety analyses

7.5 Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Significant medical history and co-morbidities
- Concomitant therapies
- Other characteristics as appropriate

7.6 Primary Analysis

The primary objective of this study is to determine the 2-year disease free survival (DFS) of patients with resected, early stage NSCLC and activating *EGFR* mutations that are treated with 2 years of adjuvant erlotinib. 2-year DFS is the percentage of patients alive and free from disease recurrence 2 years after enrollment.

7.7 Secondary Analyses

All enrolled patients treated with at least one dose of study drug and undergoing at least one radiographic study for documentation of disease status will be included in the secondary analyses. These analyses will include the following:

- Toxicity profiles and tolerability of 2 years of adjuvant erlotinib.
- Estimate of the median disease-free survival and median overall survival.
- Kaplan-Meier curves and quartiles for DFS and OS.

The overall safety profile erlotinib will be assessed by examining the number, severity, and timing of adverse events. Toxicities will be graded according to the NCI CTC version 3.0, see Appendix 4. Safety analyses will include the following:

- Summaries of the adverse event rates, by dose level
- Listings and frequency tables categorizing laboratory and nonlaboratory AEs by maximum NCI CTC grade and relationship to study drug

DFS is calculated from the date of enrollment to the date when objective tumor recurrence is observed or until death if the patient has not recurred. OS is assessed from the time of enrollment until the time of death, and surviving patients will be censored at the date they are last known to be alive.

7.8 Correlative Analyses

All enrolled patients must have tissue available for screening for *EGFR* mutations. Those who are treated with at least one dose of study drug and have sufficient and appropriate samples for analysis, either from the primary tumor or biopsy material from recurrent tumors, will be included in the correlative science analyses. These studies are aimed at defining the association of *EGFR* mutations, *EGFR* amplification, and EGFR protein expression, as well as investigating the mechanisms of resistance to adjuvant erlotinib. Correlative science analyses will include the following:

- Evaluation of the association of *EGFR* mutation with *EGFR* amplification and/or EGFR protein expression in early and relapsed disease.
- Evaluation of *EGFR* mutation status, *EGFR* amplification, *MET* amplification, and EGFR protein expression in recurrent versus primary NSCLC after treatment with adjuvant erlotinib in order to determine mechanisms of resistance.
- Evaluation of the relationship of CTCs to disease recurrence, and the relationship of the EGFR mutational status of CTCs to that of the primary and/or recurrent tumor samples

8.0 QUALITY ASSURANCE OFFICE FOR CLINICAL TRIALS (QACT) EXTERNAL SITE MONITORING PLAN

8.1 The QACT will provide the following services:

- Central Registration: All 100 of the participants accrued to protocol 07-259 will be registered through the QACT prior to beginning protocol treatment. All of the eligibility checklists and consents will be reviewed for completeness and accuracy by the QACT Protocol Registrars before registration will occur, as is standard practice.

- Data Collection and Computerization: This trial will have data collected through the electronic data collection (eDC) system, Inform. The QACT will coordinate the training of all sites on this web–based application and the QACT Data Analyst will be QA and QC'ing data that is electronically entered. This eDC system will also allow for the Overall PI and DFCI study team to view the status of data collection at all sites in a real time basis. The QACT Data Analysts will also be providing formal missing form reports on an on-going basis, as well as help prepare the data for interim and final analysis by biostatistics.

- Site Monitoring/Auditing: After a site has accrued 2-3 participants, the QACT will be conducting an on-site audit. This is anticipated to occur within the first year of enrollment. Similar to the cooperative group auditing structure, one visit to each site will be planned during the 18 month expected enrollment period of the trial. If significant violations are uncovered during the audit, a follow-up audit may be requested. The final audit reports for the external sites will be reported to the Overall PI, as well as the Audit Subcommittee, as is standard practice.

9.0 APPENDICES

Appendix 1: AJCC Seventh Edition Staging for Non-Small Cell Lung Cancer[43]

Definition of TNM:
Primary tumor (T)

- TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) . The uncommon superficial spreading tumor of any size is classified as T1 even when extending to the main bronchus, as long as the invasive component is limited to the bronchial wall.
    - T1a: Tumor ≤2 cm in greatest dimension
    - T1b: Tumor >2 cm but ≤3 cm in greatest dimension
- T2: Tumor >3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤5 cm)
        - Involves the main bronchus, ≥2 cm or more distal to the carina
        - Invades the visceral pleura
        - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
    - T2a: Tumor >3 cm but ≤5 cm in greatest dimension
    - T2b: Tumor >5 cm but ≤7 cm in greatest dimension
- T3: >7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus <2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
- A tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
- T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor
- N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

- N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1a: Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural or pericardial effusion
- M1b: Distant metastasis

Stage Grouping

Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1, T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	Any N	M0
Stage IV	Any T	Any N	M1a,b

Stage Grouping

Appendix 2: ECOG Performance Status Scale[44]

ECOG 0	Fully active, able to carry on all pre-disease performance without restrictions
ECOG 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg. light housework, office work
ECOG 2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
ECOG 3	Capable of only limited self-care, and confined to bed or chair more than 50% of waking hours
ECOG 4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
ECOG 5	Deceased

Appendix 3: Cockcroft-Gault Formula for Creatinine Clearance[45]

$$CrCl\ (mL/\min) = \frac{(140 - age\ in\ years) \times weight\ in\ kg}{Serum\ Creatinine\ (mg/100mL) \times 72} \left[for\ women,\ multiply\ by\ 0.85 \right]$$

Appendix 4: National Cancer Institute Common Toxicity Criteria

When the protocol is downloaded onto our institutions' electronic clinical protocol system, an Internet link to the NCI CTC site will be installed. This 72-page document can be viewed at http://ctep.cancer.gov. We will be using the 2003 version of the criteria.

Only selected adverse events will be collected for this study. A complete list, with CTC codes is below.

DE106	Dry skin		HP104	Pancreatitis
DE113	Nail changes		HP102	Liver dysfunction
DE115	Pruritis/Itching			
DE116	Rash/desquamation		CN101	Fatigue
DE117	Rash, acne/acneiform			
DE120	Erythema multiform		OC105	Keratitis
DE122	Skin breakdown/decubitus		OC999	Conjuntivitis
			OC120	Corneal Tearing/perforation
GI101	Anorexia		PU126	Pneumonitis
GI110	Diarrhea			
GI153	Mucositis/stomatitis		RE999	Renal failure, nos
GI169	Nausea			
GI999	GI perforation, NOS			
GI239	Vomiting			
HE113	Lower GI bleed			
HE120	Upper GI bleed			

Appendix 5: Potential CYP3A4 Inhibitors and Inducers

CYP3A4 Inhibitors
Atazanavir
Delaviridine
Indinavir
Nelfinavir
Ritonavir
Saquinavir
Amiodarone
Cimetidine
Ciprofloxacin
Clarithromycin
Diclofenac
Diethyl-dithiocarbamate
Diltiazem
Doxycycline
Erythromycin
Flucanazole
Fluvoxamine
Gestodene
Grapefruit juice
Indinavir
Isoniazid
Itraconazole
Ketoconazole
Mifepristone
Nefazodone
Nicardipine
Norfloxacin
Norfluoxetine
Mibefradil
Quinidine
Telithromycin
Troleandomycin
Verapamil
Voriconazole

CYP3A4 Inducers/EIAEDs
Aminoglutethomide
Carbamezepine
Fosphenytoin
Nafcillin
Nevirapine
Oxcarbazepine
Phenobarbital
Phenytoin
Primidone
Rifamycins
St. John's Wort

Appendix 6: Identifying and Attributing Cause to a Serious Adverse Event

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

"Life threatening" means that the patient was at immediate risk of death from the adverse event as it occurred or it is suspected that use or continued use of the product would result in the patient's death. "Life threatening" does not mean that had an adverse event occurred in a more severe form it might have caused death (ie, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered adverse events if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in a situation where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Disease progression

Any events or hospitalization that are unequivocally due to progression of disease must not be reported as serious adverse events.

FURTHER GUIDANCE ON THE ASSESSMENT OF CAUSALITY

The following factors should be considered when deciding if there is a "reasonable possibility" that an adverse event (AE) may have been caused by the investigational product. A "reasonable possibility" could be considered to exist for an AE when 1 or more of these factors exist.

- **Time course of events and exposure to suspect drug**: Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of suspect drug?
- **Consistency with known drug profile**: Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- **De-challenge experience**: Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- **No alternative cause**: The AE cannot be reasonably explained by another etiology, such as the underlying disease, other drugs, other host, or environmental factors.
- **Re-challenge experience**: Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- **Laboratory tests**: Has a specific laboratory investigation confirmed the relationship?

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply, or if there is evidence of exposure and a reasonable time course, but any de-challenge (if performed) is negative or ambiguous, or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as the following:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as having a "reasonable possibility" of causal relationship, unless additional evidence becomes available to refute this.

DFCI IRB Protocol #: 07-259

APPENDIX 7

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan (DSMP)

Data Safety Monitoring Plan Table of Contents

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations (21 CFR Part 11); Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements.

1.2 Multi-Center Data and Safety Monitoring Plan Components

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: One or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates are not viewed as outside sites in this definition.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CH, BWH) will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (FDA, OBA etc.).

DF/HCC Contract Principal Investigator: Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

Protocol Chair: The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies (FDA, OBA etc.).

Participating Institution: A participating institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The participating institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP. In addition to the Lead Institution, the Quality Assurance Office for Clinical Trials (QACT) provides support services to assist the Protocol Chair.

2.0 GENERAL ROLES AND RESPONSIBILITIES

The Protocol Chair (DF/HCC Principal Investigator), Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, Lecia Sequist, will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the protocol.
- Assure all participating institutions are using the correct version of the protocol.
- Monitor progress and overall conduct of the study at all participating institutions.
- Ensure all DFCI IRB, and DF/HCC reporting requirements are met
- Review data and maintain timely submission of data for study analysis.
- Identify participating institutions and obtain accrual commitments. The Protocol Chair will also submit a protocol attachment labeled as "Participating Investigators" to the DFCI IRB that provides the names and contact information for all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page. Revisions to the list will be submitted to the DFCI IRB as an administrative protocol amendment to reflect changes in staff and assignment of responsibility as they occur.

2.2 Coordinating Center (Lead Institution)

The Coordinating Center is the DF/HCC Lead Institution's study team or designee (i.e Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution will ensure that all participating sites within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and Health Insurance Portability and Accountability Act (HIPAA) requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution's study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of Institutional Review Board (IRB) approvals from all participating institutions.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to Protocol Chair for timely review.
- Distribute external Serious Adverse Event safety reports.
- Monitor and audit Participating Institutions either by on-site inspection of

selected participant records and/or with submitted source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration.
- Confirm eligibility and consent.
- Provide auditing services (funding and QACT approval required).

2.3 Participating Institution

The Participating Institution(s) will be identified on the title page for each protocol. In addition, each participating institution will provide to the Lead Institution or designee a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards. The general responsibilities for each participating institution are as follows:

- Commit to accrual to the Lead Institution's (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Update Coordinating Center (Lead Institution or designee) with research staff changes on a timely basis.
- Register participants through the QACT.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center (Lead Institution or designee).
- Submit Serious Adverse Event reports directly to the Coordinating Center (Lead Institution or designee).
- Submit deviations and violations to the Coordinating Center (Lead Institution or designee).
- For protocols using investigational agents, the participating institution will order their own investigational agents regardless of the supplier (i.e. NCI, pharmaceutical company).

3.0 DF/HCC QUALITY ASSURANCE OFFICE FOR CLINICAL TRIALS

The DF/HCC QACT is a unit that has been developed to collect, manage, and monitor data for DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to monitor DF/HCC trials.

3.1 Organizational Structure

The DF/HCC Quality Assurance Office for Clinical Trials administrative structure consists of:

DF/HCC Quality Assurance Officer for Clinical Trials: Oversees the functions of the DF/HCC QACT.

QACT Assistant Director for Data: Provides direct oversight to the QACT Data Analysts assigned to CRF design, data collection and computerization for DF/HCC trials.

The DF/HCC QACT Data Analysts will be assigned on a protocol by protocol basis. Each protocol's data analyst is responsible for database management, data entry, data quality assurance, and protocol specific correspondence related to the collection and quality assurance of data.

QACT Assistant Director for Monitoring: Provides direct oversight to the QACT Protocol Registrars and Clinical Research Auditors.

The DF/HCC Protocol Registrars are responsible for the confirmation of each participant's eligibility and consent prior to protocol registration.

If funded and QACT approved, the DF/HCC Clinical Research Auditors may assist the Lead Institution in their auditing responsibilities for multi-center trials. The QACT auditor is responsible for systematically evaluating participant safety, protocol compliance, institutional SOPs, ICH GCP and Federal regulation compliance, data accuracy and investigational drug handling to assure a high standard of quality for DF/HCC trials.

4.0 PROTOCOL DEVELOPMENT

4.1 Activation of a Protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting SAEs, violations and deviations per DFCI IRB guidelines and if applicable, FDA or OBA Guidelines. Further, the Protocol Chair will be the single liaison with the FDA or OBA, as applicable.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify participating institutions and obtain accrual commitments. The Protocol Chair will also submit a protocol attachment labeled as "Participating Investigators" to the DFCI IRB and if applicable FDA or OBA, that provides the names and contact information for all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating

Institutions use the correct version.

- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.
- Communicate with the site-PI's via email and periodic teleconferences as necessary, including a site initiation teleconference"

4.2 Coordinating Center Support Function

The DF/HCC Lead Institution's study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution's study staff or designee include:

- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all participating institutions in the DF/HCC Multi-center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms.
- Maintain and document communication with all participating institutions.

5.0 PROTOCOL MANAGEMENT

The Coordinating Center (Lead Institution or designee) is responsible for assuring that each Participating Institution in the DF/HCC Multi-center Protocol has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Lead Institution or designee must maintain copies of all IRB approvals, for each participating institution.

5.1 Protocol Distribution

The Coordinating Center (Lead Institution or designee) will distribute the final approved protocol and any subsequent amended protocols to all Participating Institutions.

5.2 Protocol Revisions and Closures

The participating institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the Lead Institution or designee. It is the individual participating institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating institutions will receive written notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee.

Non-life-threatening protocol revisions should be implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately.

Protocol Closures and Temporary Holds: Participating institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds, with follow-up by mail from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

5.3 Informed Consent Requirements

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is DF/HCC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials.

5.4 IRB Documentation

The following must be on file with the DF/HCC Lead Institution or designee prior to participant registration:

- Approval Letter of the institution's IRB **(**An Expedited IRB first approval is NOT acceptable)
- IRB approval for all amendments

It is the individual institution's responsibility to notify its IRB of protocol revisions. Participating institutions will have 90 days from receipt to provide the DH/HCC Lead Institution or designee their IRB approval for Major Amendments* to a protocol.

*** DF/HCC defines a Major Amendment** as: A substantive change in the study which may increase or decrease the risk to study participants. Major revisions require full IRB approval. The following criteria are examples of revisions to a protocol that are considered to be major amendments:

- Change of eligibility (inclusion/exclusion) criteria
- Change in design of protocol
- Change in statistical section
- Change in sample size/accrual (e.g., doubling the sample size)
- Change in informed consent
- Change of estimated dropout rate
- Change of treatment or intervention

- Change of device
- Change in primary objective evaluation process

5.5 IRB Re-Approval

Annual IRB re-approval from the Participating institution is required in order to register participants onto a protocol. There is no grace period for annual re-approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution or designee from the Participating Institutions on or before the anniversary of the previous approval date.

5.6 Participant Confidentiality and Authorization Statement

The Health Insurance Portability and Accountability Act of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which has modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol participating institutions) must use.

The DF/HCC Multi-Center Protocol will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

5.7 Participant Registration

To register a participant, the following documents should be completed by the DF/HCC Multi-Center Protocol participating site and faxed to or e-mailed to the Lead Institution designee:

[redacted]

To ensure proper review of eligibility documents, please send all information no later than 2pm EST. Prior approval is needed for same day, intent to treat registrations.

- Copy of required laboratory tests: WBC, plt, hemoglobin, bilirubin, ALT, AST, serum creatinine, result of tumor EGFR mutation testing
- Copy of baseline medical exam that contains the following: Date of original diagnosis; surgery date and type of surgery; PS; histology; Stage of disease (1A-IIIA); smoking status; EGFR mutation status/results and prior treatment including chemotherapy and radiation.
- Signed informed consent form
- HIPAA authorization form (if separate from the informed consent document)

The research DF/HCC Multi-center Protocol participating site will then call or e-mail the Lead Institution or designee to verify eligibility. To complete the registration process, the Lead Institution or designee will:

- Register the participant on the study with the DF/HCC Quality Assurance Office for Clinical Trials (QACT)
- Fax or e-mail the participant case number, and if applicable the dose treatment level, to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration

5.8 DF/HCC Multi-center Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and written on all data and QACT correspondence for the participant.

5.9 DF/HCC Multi-center Protocol Registration Policy

5.9.1 Initiation of Therapy: Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the participant's Registration Confirmation memo from the DF/HCC QACT. Therapy must be initiated per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy.

5.9.2 Eligibility Exceptions: The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

5.9.3 Verification of Registration, Dose Levels, and Arm Designation: A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one working day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

5.9.4 Confidentiality: All documents, investigative reports, or information relating to the participant are strictly confidential. Any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

5.10 Schedule of Data Submission

The DF/HCC QACT develops a set of electronic case report forms, (CRF/eCRFs) for use with the DF/HCC Multi-Center Protocol. These forms are designed to collect data for each study. Prior to the registration of the first patient, the Participating Institution will designate a study coordinator(s) that will be trained using the DF/HCC data capture system, INFORM. Registration/accrual can not occur without a trained study coordinator. The schedule for submission of case report forms to the DF/HCC QACT is generally specified in each protocol. When not specified in the protocol, the DF/HCC QACT will require the forms to be submitted as follows:

COMMON FORMS & REPORTS

- Eligibility Checklist, (Informed Consent/ Participant Authorization for the Release of Personal Health Information)
- On-study Form
- Baseline Assessment Form (Baseline disease assessment/measurement)
- Treatment Forms
- Adverse Event Forms
- Response Assessment Form (Follow-up disease assessment/Measurement)
- Off-Treatment/Off Study Form
- Follow-Up/Survival Forms

Note: It is necessary to send only ONE copy of all paper Case Report Forms.

5.10.1 Eligibility Checklist

Purpose - Outlines protocol-specific eligibility criteria and includes the following:

Participant Demographics (sex, race, ethnicity, initials, date of birth)

1) Parameters for eligibility
2) Parameters for exclusion
3) Parameters for stratifications

If a time frame is not specified in the protocol, tests must be completed as follows:

- Lab tests required for eligibility must be completed within 14 days prior to study enrollment by the QACT.
- Non-lab tests required for eligibility must be performed within 30 days prior to study entry. Example: radiological scans

- **Schedule for Submission -** Completed prior to participant registration. The Informed Consent/ Participant Authorization for the Release of Personal

Health Information should be submitted with the Eligibility Checklist at the time of registration.

5.10.2 On-study Form (includes: Study entry, prior therapy and baseline assessments)

Purpose - documents the following items:

- Demographic data
- Prior therapy
- Past medical and surgical history
- Description of participant's physical status at protocol registration
- Disease site specific data

Schedule for Submission - Submitted to DF/HCC QACT within 14 days after registration.

5.10.3 Baseline Assessment Form

Purpose – Documents objective and subjective disease status as defined by the protocol**.** Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

Schedule of Submission – Submitted within 14 days after registration.

5.10.4 Treatment Form

Purpose - Records the following information related to the time the participant receives protocol treatment:

- Participant, Protocol, Affiliate information
- Protocol treatment and supportive therapy per treatment cycle
- Protocol specific laboratory values per treatment cycle
- All medications other than protocol chemotherapy agents used to treat concomitant diagnoses, if applicable

Schedule for Submission – Submitted within 10 days after the last day of the cycle.

5.10.5 Adverse Event Report Form

Purpose – Documents adverse events that occur while the participant is receiving treatment and for up to 30 days after the last dose of treatment. All adverse events are to be graded by number using the toxicity grading scale required by the protocol. Only selected adverse events are being followed. Please, refer to the protocol for a complete list. This form is not for IRB submission, but for recording the AE in the research database.

Schedule for Submission – Submitted within 10 days after the last day of the cycle.

5.10.6 Response Assessment Form

Purpose – Documents objective and subjective response as defined by the protocol. Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

Schedule of Submission – Submitted within 10 days after the completion of the cycle required for response evaluation.

5.10.7 Off Treatment/Off Study Form

Purpose - The Off Treatment/Off Study Form is submitted when the participant is removed from the study or has completed all protocol treatment. Note: If the participant dies while on protocol**,** the Off Study Form is the last form submitted.

Schedule of Submission – Submitted within 14 days after completing treatment or taken off study for any reason.

5.10.8 Follow up / Survival Form

Purpose - Summarizes participant status at a given point in time after being removed from treatment.

Schedule of Submission – Submitted within 14 days after the protocol defined follow up visit date or call.

5.11 Data Form Review

When data forms arrive at the DF/HCC QACT, they are reviewed for:

Timeliness:
Did the form arrive on time as specified in the protocol?

Completeness:
Is all the information provided as required per protocol?

Participant Eligibility:
Does the participant meet the eligibility requirements for the study based on the demographic data, lab values and measurements provided?

Stratification:
Are the stratification parameters consistent with what was given at the time of registration?

Protocol Treatment Compliance:
Was the patient compliant with the study medication? The patient diary should be reviewed and old drug returned at each visit. Documentation of compliance should be captured in subject's medical record although there is not a data form for this information.

Adverse Events (Toxicities):
Did the participant experience adverse events (toxicities or side effects) associated with the treatment? Was the treatment delayed due to the adverse event? What was the most severe degree of toxicity experienced by the participant?

Notations concerning adverse events will address relationship to protocol treatment for each adverse event grade. All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Criteria assigned to the protocol and all adverse events must be noted on the participant's Adverse Event (Toxicity) Forms.

Response:
Did the participant achieve a response? What level of response did they achieve? On what date did the participant achieve the response and how was the response determined?

Response criteria are defined in the protocol. A tumor assessment must be performed prior to the start of treatment and while the participant is on treatment as specified by the protocol.

Objective responses must have documentation such as physical measurements, x-rays, scans, or laboratory tests.

A subjective response is one that is perceived by the participant, such as reduction in pain, or improved appetite.

5.12 Missing and Deficient Memorandum

Data submissions are monitored for timeliness and completeness of submission. Participating institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written query from the DF/HCC QACT Data Analyst. Responses to the query should be completed and returned within 14 days. Responses may be returned on the written query or on an amended case report form. In both instances the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the participating institution will receive a Missing Form Report from the DF/HCC QACT noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of three times a year.

6.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is to be done by each site directly via Genentech/OSI.

Each site should check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

7.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria assigned to the protocol (CTCAE Version 3.0) and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB).

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

7.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience 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 serious when, based upon appropriate medical judgment, they may jeopardize the participant or 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 in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

Unless otherwise specified in the protocol, the study will utilize the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 for Toxicity and Adverse Event reporting. A copy of the CTC or CTCAE Criteria can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

7.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs) will be followed as is delineated in the protocol.

In addition, the Participating Institutions must report the serious adverse events to the Protocol Chair and the Coordinating Center (Lead Institution) at the time SAEs are submitted.

The Lead Institution will maintain documentation of all Adverse Event Reporting and be responsible for communicating all SAEs to all Participating sites.

8.0 PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all institutions participating in the DF/HCC Multi-center Protocol.

8.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

8.2 Reporting Procedures

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record to describe all protocol deviations and violations.
The Protocol Chair will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair and Lead Institution or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the participating site's own IRB, per its policy.
Protocol violations occurring at a participating institution will be submitted to that site's own IRB. A copy of the participating institution's IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by mail, facsimile, or via e-mail within 10 business days after the original submission.

Coordinating Center: Upon receipt of the violation/deviation report from the participating institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the participating institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

9.0 QUALITY ASSURANCE

1) The quality assurance process for a clinical trial research study requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality assurance oversight for the DF/HCC Multi-center Protocol.

9.1 Ongoing Monitoring of Protocol Compliance

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. The Lead Institution or designee and if applicable QACT Data Analysts assigned to the Protocol will perform the ongoing protocol compliance monitoring with the support of the participating institution's Coordinators, the Principal Investigators, and the Protocol Chair.

9.2 Evaluation of Participating Institution Performance

9.2.1 Eligibility Checklist: Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC QACT prior to registration on protocol. The checklist and informed consent document are reviewed by a DF/HCC QACT Protocol Registrar before the participant can be registered on a protocol. The DF/HCC QACT cannot make exceptions to the eligibility requirements.

9.2.2 Accrual of Eligible Participants: Annual accrual rates for eligible participants enrolled onto therapeutic clinical trials is calculated for each institution. Institutions are expected to maintain the minimum annual average accrual as defined by the protocol grant or contract.

9.3 On-Site Auditing

9.3.1 DF/HCC Sponsored Trials

For all DF/HCC sponsored protocols:
The participating institutions may be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Also, the participating institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution or designee.

After a site has accrued 2-3 participants, the QACT will be conducting an on-site audit. This is anticipated to occur within the first year of enrollment. If significant violations are uncovered during the audit, a follow-up audit may be requested. The final audit reports for the external sites will be reported to the Overall PI, as well as the DF/HCC Audit Committee, as is standard practice.

9.3.2 Participating Institution

It is the participating institution's responsibility to notify the DF/HCC Lead Institution or designee of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

9.3.3 Coordinating Center (Lead Institution or designee)

The Protocol Chair will review all DF/HCC Multi-Center Protocol Final Audit reports and corrective action plans if applicable. The Lead Institution or designee must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Subcommittee. Based upon the audit assessments the DF/HCC Audit Subcommittee could accept or conditionally accept the audit rating and final report. Conditional approval could require the Protocol Chair to implement recommendations or require further follow-up. For unacceptable audits, the Audit Subcommittee would forward the final audit report and corrective action plan to the Clinical Investigations Policy and Oversight Committee and the DFCI IRB as applicable.

9.4 Sub-Standard Performance

The Protocol Chair, and DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

9.4.1 Corrective Actions: Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, and adherence to protocol requirements will be recommended for a six- month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.

10.0 REFERENCES

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Study Drug Log

Please indicate the date, time, drug taken and dosage on the following chart

Drug A: **Erlotinib**

Date	Time	Drug A	Dose

Symptoms

Please indicate any symptoms that you may experience during your treatment. Include the date that your particular symptom started and when it ended. Please grade your symptoms according to the following scale:

Grade 1 = **Minimal:** you are aware of the symptoms, but they did not interfere with normal activities

Grade 2 = **Mild:** the symptom disrupted normal routine, but required activities were accomplished

Grade 3 = **Moderate:** the symptom prevented normal activities, but was manageable with prescribed therapies at home

Grade 4 = **Severe:** the symptom required you to seek further medical intervention

Symptom			
	Start Date	End Date	Grade

The toxicity grade should reflect the most severe level experienced during the same time period.