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Title: Afatinib Sequenced with Concurrent Chemotherapy and Radiation in EGFR-Mutant Non-Small Cell Lung Tumors: The ASCENT Trial.

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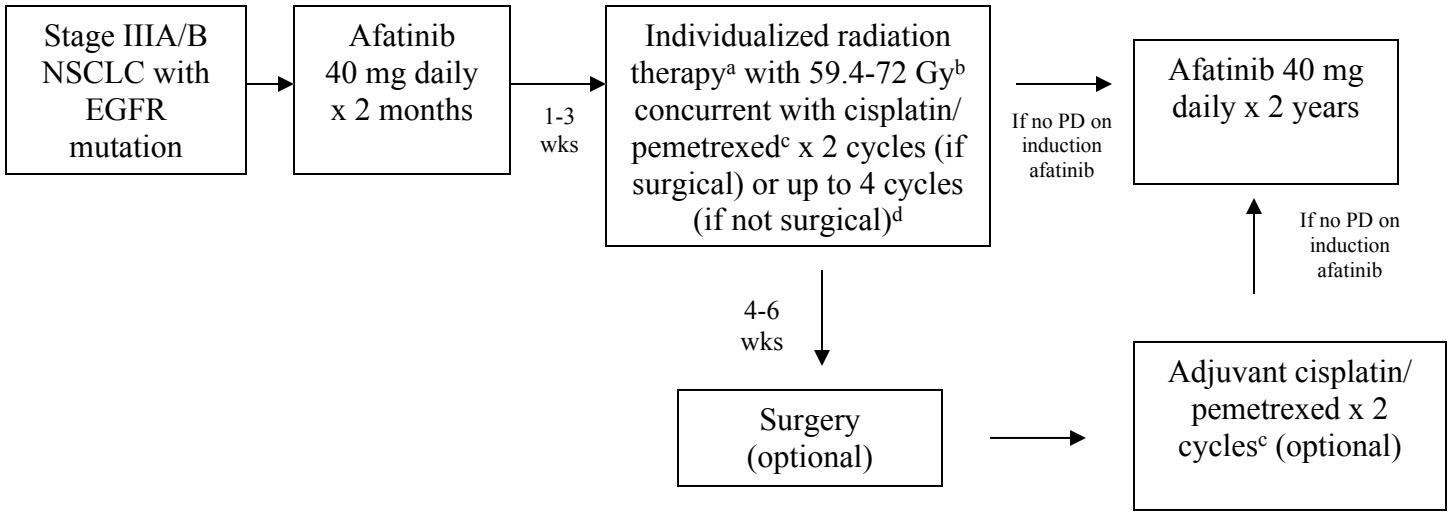
Agent(s):
Cisplatin, generic (no IND)
Pemetrexed, (no IND) – commercial supply from Eli Lilly
Afatinib, IND# 115009 – Boehringer Ingelheim Pharmaceuticals, Inc
Radiation Therapy (no IND)

SCHEMA



a. Individualized radiation consists of 4D CT-planned conformal radiation therapy with individualized dosing 59.4-72 Gy (see Section 5.3.4).
b. If a patient is deemed a candidate for surgical resection either before or during the radiation course, the dose will be limited to no more than 54 Gy (see Section 5.3.4).
c. Cisplatin 75 mg/m^2, pemetrexed 500 mg/m^2; every 3 weeks
d. If no surgery is planned and patient is being treated with definitive chemoradiation, any cycles of chemotherapy given after RT is complete are referred to as adjuvant chemotherapy.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

Locally advanced non-small cell lung cancer (NSCLC) comprises approximately 30% of all patients with NSCLC and includes stages IIIA and IIIB. Standard of care for this heterogeneous group of patients is multimodality therapy with chemotherapy and radiation, with the possible addition of surgical resection for operable candidates. Although locally advanced disease is considered curable, outcomes are poor with median progression-free survival of 10-13 months, median overall survival 17-24 months, and 2 year-survival about 50% (1-3).

Recently there has been interest in including targeted therapy into the upfront treatment of patients with locally advanced NSCLC given the success of these drugs in the metastatic setting. Notably, a recent study added gefitinib, a tyrosine kinase inhibitor (TKI) to the epidermal growth factor receptor (EGFR) to chemotherapy and radiation in unselected patients with locally advanced NSCLC and found no benefit to the addition of the targeted agent (4). However, in the advanced disease setting it is clear that it is those patients with an EGFR mutation that derive the most benefit from treatment with an EGFR TKI (5-8). The utility of EGFR TKIs in locally advanced, potentially curable EGFR mutant disease remains to be established.

The efficacy of radiation is limited by the typically large tumor size encountered in stage III disease. While EGFR TKIs have radiosensitizing properties, there is concern that concurrent administration of TKI with radiation has the potential for severe toxicity (9, 10). In contrast, induction TKI alone is not expected to enhance radiation side effects but may provide substantial cytoreduction prior to radiation, thereby increasing the ability of a given dose of radiation to achieve locoregional tumor control.

Afatinib is a potent, irreversible small molecule tyrosine kinase inhibitor that targets EGFR and HER2. A phase II study of patients with EGFR-mutated advanced NSCLC has shown promising results with a response rate of 43-62% (11), however the *de novo* response rate to genotype-directed therapy in earlier stage EGFR-mutant NSCLC has not been previously studied. We therefore propose to use afatinib as induction therapy prior to standard therapy with concurrent chemotherapy and radiation with or without surgery in this patient population to determine the response rate to the single-agent drug.

Thirty patients with locally advanced NSCLC harboring an EGFR mutation will be enrolled. Participants will be treated with 8 weeks of induction afatinib, after which time imaging will be performed to determine the response rate to induction therapy. This will be followed by standard therapy for locally advanced disease, i.e., concurrent cisplatin, pemetrexed and individualized 4D conformal radiation therapy with or without surgical resection. In order to minimize toxicity and maximize potential benefit, a personalized consolidation period will proceed: patients who did not have progression during induction afatinib will receive 2 years of consolidation afatinib, whereas those who progressed during induction therapy will not receive further treatment and will enter a surveillance mode. We hypothesize that the

response rate to induction afatinib will be equivalent to or greater than the response rate seen in the metastatic setting.

1.2 Primary Objective

To assess the response rate to induction afatinib.

1.3 Secondary (Exploratory) Objectives

1. To estimate the 2-year progression-free survival (PFS) of stage III EGFR mutation-positive patients treated with this novel regimen of induction afatinib, cisplatin/pemetrexed and radiation, with or without surgery, and selected consolidation afatinib.
2. To describe the safety profile of combining induction afatinib therapy with concurrent chemotherapy and radiation.
3. To estimate the proportion of patients with unresectable disease that can be converted to operable cases.
4. To estimate 2-year locoregional tumor control rates, distant metastasis rates and overall survival rates, as well as median overall survival (OS).
5. To evaluate genomic tumor DNA for the presence of pre-existing resistance mechanisms such as EGFR T790M mutations or MET kinase amplifications, and explore correlations of these with response to afatinib and to explore additional predictive biomarkers of tumor response to afatinib and chemoradiation in clinical samples and circulating tumor cells (including chromatin markers and DNA repair proteins).

2. BACKGROUND

2.1 Study Agent(s)

2.1.1 Afatinib

Afatinib is a potent, irreversible small molecule inhibitor of the erbB-family of tyrosine kinase receptors EGFR (erbB1/HER1) and HER2 (erbB2). It appears equally active in EGFR-mutant NSCLC as historical comparison to gefitinib, and is gaining an increasing role in genotype-directed therapy (11). Importantly, given its' irreversibly-binding chemistry, it has the potential to overcome the T790M resistance mutation which arises in approximately 50% of EGFR-mutated NSCLCs treated with reversible EGFR TKIs (12-14). The activity of afatinib against EGFR-mutated tumors was demonstrated in Lux-Lung 2, a phase II study of patients with advanced disease who were treated with afatinib at a dose of 40 mg daily (11). Tumor size reduction was seen in 90% of patients and response rates ranged from 43% to 62% depending on the particular EGFR mutation detected.

The absolute bioavailability of afatinib after oral ingestion was 45% in rates with a median tmax reached after 4 hours and a terminal half-life of 4.5 hours (15). There was no relevant inhibition of cytochrome P450 detected. Afatinib is primarily excreted in the feces. It is well-tolerated with the most common side effects similar to other EGFR TKIs including diarrhea, nausea, vomiting, rash stomatitis, and fatigue (16).

2.1.2 Cisplatin (17)

Cisplatin is a platinum-containing complex which crosslinks DNA, resulting in DNA strand breakage and cell death. The parent compound is excreted in the urine and exceeds the creatinine clearance. Clearance of free platinum by the kidney is nonlinear and variable depending on dose, urine flow rate, and individual variability. There is no significant relationship between creatinine clearance and renal clearance of either free platinum or cisplatin. Side-effects of cisplatin include renal toxicity, ototoxicity, and nausea/vomiting but is a widely-used chemotherapeutic agent in the treatment of various solid tumors. For more information, please see cisplatin package insert.

2.1.3 Pemetrexed (18)

Pemetrexed is a folate analog that exerts its antineoplastic activity by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is approved for use in non-squamous NSCLC for initial treatment in combination with cisplatin and as a single-agent after prior chemotherapy. It is also the only approved agent in combination with cisplatin for use in malignant pleural mesothelioma. Side effects include fatigue, nausea, vomiting, constipation, anorexia, cytopenias, and stomatitis. For more information, please see pemetrexed package insert.

2.2 Study Disease

2.2.1 Stage III NSCLC

Lung cancer is the second most common cancer and the most common cause of cancer death among men and women in the United States (Jemal 2010). Lung cancers are divided histologically into small cell lung cancer (SCLC) and NSCLC, with NSCLC accounting for over 80% of cases (19). Approximately 30% of patients who are newly diagnosed with NSCLC have stage III, or locally advanced disease. Even favorable, marginally resectable stage IIIA (N2) NSCLC has a 5-year OS rate of only 27% with aggressive trimodality therapy consisting of chemotherapy, radiation to 45 Gy, and surgery (3). Unfortunately, the majority of patients with stage III NSCLC will relapse, at which time their disease becomes incurable. Improving the success of the upfront treatment of patients with marginally resectable stage III disease is therefore critical to improving survival.

Historically, because local failure rates after radiation-based therapy is high in stage III patients, surgical resection has been frequently employed, particularly at high-volume surgical centers and among those patients with lower tumor and nodal disease burden. In the Intergroup 0139 randomized phase III trial, trimodality therapy has yielded an isolated local failure rate of 10%, and median OS, 2-year OS, and 5-year OS rates of approximately 23 months, 50%, and 27%, respectively (3). Median PFS in the trimodality arm was 12.8 months, which was significantly better than 10.5 months in the non-surgical arm. However, there was no statistically significant difference in OS, with a median OS time of 22.2 months for non-operative patients and 23.6 months for surgical patients. With local and distant failure high even among patients with favorable disease treated aggressively with chemotherapy, radiation therapy, and surgical resection, many attempts have been made to improve upon this algorithm. However, none has become standard of care given the lack of survival benefit.

Over the last several years it has become apparent that patients with NSCLC can be subdivided based on molecular characteristics of the tumor. In the setting of advanced NSCLC, testing for the genetic status of the EGFR oncogene has been introduced into clinical practice to guide the selection of patients for treatment with EGFR tyrosine kinase inhibitors TKIs. Treatment with an EGFR TKI in patients with advanced NSCLC harboring an EGFR mutation results in a higher response rate and improved progression-free survival compared to treatment with standard chemotherapy (5-8). However, even in patient with advanced NSCLC harboring an EGFR mutation who derive benefit from an EGFR TKI, resistance to the drug develops within approximately 1 year, most commonly due to the development of a T790M resistance mutation or MET amplification (12-14). There is little data regarding the incorporation of EGFR inhibitors in patients with stage III EGFR mutation-positive NSCLC. A recent study adding consolidation EGFR TKIs to standard chemotherapy and radiation has raised questions about the safety of this approach, including the possibility of detrimental outcomes (4). However, this study was performed in unselected patients (i.e. not chosen for inclusion based on mutation status), which leaves the question regarding the use of EGFR inhibitors in EGFR-mutated NSCLC unanswered. In addition, the use of an EGFR TKI that can overcome the T790M mutation has not yet been studied in this setting, and may result in a longer duration of activity which could then translate to improved patient outcomes.

2.2.2 Treatment-predictive biomarkers in NSCLC

To appropriately diagnose our patients on a molecular basis, the MGH has implemented a PCR-based multiplex platform (SNaPshot) performed on paraffin-embedded tissue to test for alterations in 58 commonly mutated loci in 13 oncogenes: *EGFR*, *K-RAS*, *N-RAS*, *APC*, *BRAF*, *FLT3*, *JAK2*, *Kit*, *Notch*, *PI3K*, *PTEN*, *TP53*, and *beta-catenin* (20)(20). Predictive biomarkers will eventually be used to guide the application of many types of targeted agents by identifying the subset(s) of patients most likely to benefit from the treatment approach.

Given the recent developments in our understanding of how resistance to EGFR TKIs develop, including the emergence of the EGFR T790M mutation, MET kinase amplification, and some instances of dramatic changes in tumor histology, it has become increasingly important to analyze patient's tumors for the mechanism of resistance at the time of disease progression (14). Interestingly, there is evidence that genetic resistance aberrancies may exist at low levels earlier in the course of disease and are clonally selected by the use of an EGFR TKI (21, 22). Therefore, analyzing baseline tumor DNA for the presence of small quantities of pre-existing resistance mechanisms may yield important information regarding the potential development of resistance in the future.

In addition, it is increasingly appreciated that the activity of cellular DNA damage response and repair pathways determine the sensitivity of tumors to radiation and many chemotherapeutic agents (23, 24). Functional assays have been developed to assess the activity of these pathways in live tumor tissues (25) and may yield protein or genomic biomarkers for use in future studies.

Stage III NSCLC patients offer a unique opportunity to prospectively collect tissue for the exploration of potential biomarkers of targeted agent as well as radio- and chemosensitivity. A robust effort to collect and study the tissue from patients on this trial is crucial to pave the way for future genotype-correlated treatment regimens in locally-advanced NSCLC.

2.3 Rationale for Treatment Combinations

With the ultimate goal of building the optimal stage III treatment regimen for patients with EGFR-mutant NSCLC around the foundation of an EGFR TKI, this phase II study will assess a novel combination of therapies utilizing the most targeted multi-modality strategies available with careful assessment of correlative biomarkers of both outcome and toxicity.

Rationale for the inclusion of radiation and chemotherapy: Clinical experience in stage IV disease indicates that EGFR TKI monotherapy leads to tumor response, but is not curative. Similarly, laboratory data indicate that EGFR TKI monotherapy cannot completely eradicate all EGFR-mutant tumor cells (26). Hence, EGFR TKI monotherapy for stage III disease is not a plausible therapy if the goal is cure. Chemotherapy and radiation are the backbone of the standard of care approach to stage III NSCLC in unselected patients (see Section 2.2.1). Cell line data and our own clinical research indicate the EGFR mutations render NSCLC hypersensitive to radiation (27, 28) and clinical data indicate that patients with EGFR mutations are more sensitive to chemotherapy than those that are EGFR wild-type (6, 29). Therefore, combining an EGFR TKI such as afatinib with an appropriate combination of radiation and chemotherapy should constitute the approach with the highest possible cure rate for patients with EGFR mutations.

Rationale for the choice of chemotherapy back bone: Pemetrexed, an anti-folate chemotherapeutic, is now a central player in the treatment of adenocarcinoma of the lung, given its superior efficacy in patients with advanced disease and adenocarcinoma histology as well as its favorable toxicity profile (30). Several small, single arm trials have examined the safety of platinum/pemetrexed with radiation and have found it to be well tolerated at full systemic doses (31, 32)(33). A definitive phase III randomized trial comparing radiation along with either cisplatin/etoposide or cisplatin/pemetrexed is ongoing for patients with non-squamous inoperable stage III NSCLC (the PROCLAIM study, Clinicaltrials.gov Identifier NCT00686959). Additionally, CALGB 30407 has demonstrated that the combination of radiation with concurrent pemetrexed/carboplatin with or without cetuximab has an acceptable safety profile (34), with median survival comparable to prior studies (35). Subgroup analyses from a phase III clinical trial in patients with advanced NSCLC suggests that pemetrexed works preferentially in patients with non-squamous NSCLC (30), and thus has been FDA-approved for patients with tumors of this histology. Thought leaders in the field of thoracic oncology expect that pemetrexed-based chemoradiotherapy will soon be the standard-of-care for stage III adenocarcinoma given its impressive activity in the metastatic setting as well as its improved toxicity profile. Therefore, we propose to use 4 cycles of cisplatin/pemetrexed concurrently with radiation.

Rationale for sequencing afatinib with chemo/radiation: As discussed above, afatinib is a potent, irreversible small molecule tyrosine kinase inhibitor that targets both EGFR and HER2. Given the irreversible binding of the drug to its molecular target, it may overcome the T790M resistance mutation that results in progression of disease in patients on a reversible EGFR TKI such as erlotinib or gefitinib. Afatinib has a high tumor response rate in those with stage IV EGFR-mutant NSCLC (11), and therefore this drug will be incorporated as an induction agent for stage III EGFR mutation-positive patients. This genotype-specific agent is placed in the first portion of this multi-step treatment regimen since it has the best chance of reducing the bulk of the primary tumor as well as simultaneously sterilizing micro-metastatic disease sites. After afatinib induction, cisplatin/pemetrexed and radiation will be administered. Afatinib will not be given concurrently with radiation due to the risk of unexpected severe toxicity, such as pneumonitis and esophagitis. If patients have such a regression that surgery is thought to be beneficial, resection will be allowed.

Finally, consolidation afatinib will be directed toward those patients with the most chance of benefitting from it, any patient with tumor shrinkage including 0% change on RECIST can proceed to consolidation, while any patient with RECIST growth of 1% or more is not eligible. This will be done in a personalized fashion to minimize the possibility of any detriment from consolidation or adjuvant EGFR TKI.

Rationale for correlative science studies:
There is a need to identify the subgroup of patients with EGFR mutant disease whose tumor will not respond to afatinib. In addition, it will be important to explore means by which the radio- and chemosensitivity of EGFR mutant tumor cells can be enhanced further. We will thus collect pre-treatment biopsies and circulating tumor cells (CTCs) on all patients. Using recently established assays, we will interrogate tumor specimens for functional defects in DNA repair pathways, which may render the affected tumors sensitive to DNA damaging agents such as radiation or cisplatin. In addition, we will continue to explore pre-clinical cell line models of TKI resistance to identify biomarkers of non-response that could be studied in clinical samples (funded by the DF/HCC SPORE in Lung Cancer). Altogether, these studies should help us to further refine the subgroup of patients that will derive benefit from afatinib and thereby increase the rate of cures without complications for this deadly disease.

2.4 Rationale for Radiation Dosing and Modern Radiation Techniques

Rationale for 4-Dimensional (4D) CT Based Radiation Planning
In this era of conformal therapy and intensity-modulated radiation therapy (IMRT) (see below), there is an increased desire to raise the dose to the tumor to facilitate improved survival and decrease normal tissue dose to reduce treatment-related complications. Patient setup accuracy and internal organ motion limit our ability to reduce margins (36). Especially to include intrafractional respiratory motion, large geometric expansions of the target volumes have been traditionally applied. These expansions are usually not patient-specific but rather are based on clinical experience or published margin guidelines reported in the literature. A geometric miss is still possible if tumor motion is greater than the assumed average motion. In addition, there can be unnecessary irradiation of normal tissue if tumor motion is smaller than expected. Furthermore, motion during the acquisition of images for treatment planning using a conventional helical CT scanner (3D planning) may cause artifacts, which result in distortion of the target volume and incorrect positional and volumetric information (37). Therefore, 4D CT imaging and treatment planning has been implemented at many institutions. This process involves the acquisition of a sequence of CT image sets over consecutive segments of a respiratory cycle, which cannot only identify the true tumor shape, but also define the volume occupied by the moving target (the internal target volume, ITV) (38). Respiratory motion not only applies to parenchymal tumors but also to lymph node stations. In a recent report from the MGH, the mean and maximum craniocaudal peak-to-peak motion for hilar/mediastinal nodes was 5 and 15 mm, respectively (39). Therefore, 4D CT planning will be required for the current trial.

Elective Nodal Irradiation (ENI)
Before the introduction of 3D conformal radiation therapy, standard treatment practice in the United States was to administer 40 to 50 Gy to the electively irradiated regional nodal areas (bilateral hilar and mediastinal, and, occasionally, supraclavicular areas) with an additional 20 Gy delivered to the primary tumor through reduced fields. More recently, ENI has been increasingly abandoned in dose-escalating studies incorporating modern technology (RTOG 0617) (40-42). This has several reasons, including improved

chemotherapy, improved imaging of lymphatic tumor spread with high resolution CT and PET scanning, incidental doses to uninvolved nodal drainage areas, and the consideration that irradiating clinically uninvolved nodal areas electively or prophylactically may not be rational when the gross tumor is difficult to control. In addition, several reports have consistently demonstrated that the incidence of isolated nodal failure is < 10% (40, 43, 44). In a recently reported prospective randomized trial, the use of involved field radiation yielded a better survival outcome than the ENI arm, though for involved field radiation higher total doses were utilized (45). Again, isolated nodal failure rates were low at 7%. However, it is important to keep in mind that lung cancer patients suffer from multiple causes of competing mortality and thus may die of local failure, distant failure, or intercurrent illness without detection of isolated elective nodal failures. Persistent subclinical nodal disease may also give rise to hematogenous tumor spread. Lastly, there is ample surgical literature describing the prominent hilar and mediastinal nodal spread of NSCLC, which would suggest that larger target volumes resembling the extent of surgical dissection should be used (44). While the issue of ENI remains unresolved, limited ENI based on the known published spread patterns of primary tumors will be allowed in the current trial (44, 46), as long as the maximal achievable dose to the gross tumor is not compromised.

Radiation dosing for stage III NSCLC

The nationally accepted standard radiation dose for locally advanced staged III NSCLC has remained at the same level (60-63 Gy) for more than 30 years (47, 48). However, these doses are insufficient for controlling the typically large lung tumors encountered at initial presentation, and associated local failure rates can be as high as 85% (49). Accordingly, there have been various efforts to escalate the dose of radiation to 70 Gy and higher. There are now prospective data from several groups showing that 74 Gy is tolerable in the setting of concurrent chemotherapy. RTOG 0117 determined that 74 Gy was the maximally tolerated dose (MTD) in the context of concurrent weekly carboplatin and paclitaxel (40). Similarly, a CALGB trial and a trial from the University of North Carolina determined 74 Gy to be the MTD (41, 42). Preliminary results from these trials revealed median OS times of 21.6-37 months. The RTOG is currently conducting a randomized phase III trial comparing 74 Gy to 60 Gy at 2 Gy/fraction in patients with inoperable stage III NSCLC (RTOG 0617), which is powered to detect an increase in median OS from 17 months to 24 months.

Importantly, the increasing understanding of normal tissue tolerance to radiation based on the volume of tissue receiving a certain amount of radiation has allowed an individualized approach of radiation dosing whereby the maximum dose of radiation that can be given in an individual patient is dictated by normal tissue dose-volume relationships. Radiation therapy can be individualized further by utilizing 4D CT based treatment planning, which takes into account the individual respiratory tumor motion, and conformal radiation techniques, such as intensity-modulated radiation therapy (IMRT), which conforms the dose around the individual tumor and maximizes sparing of adjacent critical normal structures such as lungs, esophagus, heart, and spinal cord[57]. It is also well established that increasing tumor sizes require increasing doses of radiation to maintain a high local control probability (50). Because radiation will be combined with

chemotherapy at systemic doses rather than the more easily tolerated weekly carboplatin/paclitaxel regimen, the maximum dose of radiation should be < 74 Gy. Therefore, we will utilize 4D conformal radiation therapy to tailor the dose prescription to the individual patient, over a range of 59.4-72 Gy covering dose, with the maximal achievable dose principally limited by normal tissue constraints. In patients whose disease is deemed surgically resectable at any point prior to the 6th week of radiation, the total radiation dose will be limited to 45-54 Gy.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have histologically confirmed stage IIIA or IIIB non-squamous NSCLC (AJCC 7th edition). Patients with a clinical stage of IIIB are allowed only if they are thought to be a candidate for concurrent chemoradiation.

3.1.2 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral CT scan.

3.1.3 Participants must have a lung cancer harboring an EGFR mutation

3.1.4 Pulmonary function tests within 6 months of study enrollment must have FEV1 ≥ 1.2L and DLCO ≥ 40% of predicted. Patients with FEV1 of < 1.2 L but a predicted value of ≥ 40% may be eligible after review of the case by the Study Radiation PI or his designee.

3.1.5 PET/CT scan including neck, chest, abdomen, pelvis within 4 weeks of study enrollment documenting the absence of distant metastases.

3.1.6 Brain MRI with gadolinium within 4 weeks of study enrollment demonstrating the absence of brain metastases. If an MRI is medically contraindicated or if the patient refuses, a head CT with IV contrast is acceptable.

3.1.7 Age at least 18 years old. Because no dosing or adverse event data are currently available on the use of cisplatin and pemetrexed in participants < 18 years of age, children are excluded from this study.

3.1.8 Life expectancy of greater than 6 months.

3.1.9 ECOG performance status ≤ 1 (see Appendix B).

3.1.10 All patients must be evaluated by a medical oncologist, radiation oncologist, and thoracic surgeon within 4 weeks of enrollment into study to document that they

are a candidate for chemoradiation and whether or not they are candidates for consideration of surgical resection (not required to be a surgical candidate).

3.1.11 Women of child-bearing potential must have a negative pregnancy test during screening. The effects of cisplatin, pemetrexed, and radiation therapy on the developing human fetus are known to be teratogenic. For this reason women of child-bearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation (see section 5.6 for details). Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Prior EGFR tyrosine kinase inhibitor therapy (including gefitinib, erlotinib, or any experimental EGFR TKI agent)

3.2.2 Prior treatment with radiation to the thoracic region)

3.2.3 Participants may not be receiving any other investigational agents.

3.2.4 Known pre-existing interstitial lung disease.

3.2.5 Significant or recent gastrointestinal disorders with diarrhea as a major symptom (e.g. Crohn's disease, malabsorption, or CBC grade ≥2 diarrhea of any etiology).

3.2.6 History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia, or myocardial infarction within 6 months prior to randomization.

3.2.7 Any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the study drug.

3.2.8 Abnormal organ or marrow function as defined below:

- Absolute neutrophil count (ANC) < 1,500/mcL
- Platelets ≤ 100,000/mcL
- AST (SGOT)/ALT (SGPT) ≥ 3 times the upper limit of normal (if related to liver metastases ≥ 5 times the upper limit of normal)

- Total bilirubin ≥ 1.5 mg/dL (>26 mol/L, SI unit equivalent)
- Serum creatinine ≥ 1.5 times the upper normal limit or calculated/measured creatinine clearance ≤60 mL/min

3.2.9 Women of childbearing potential, or men who are able to father a child, unwilling to use a medically acceptable method of contraception during the trial. Pregnant women are excluded from this study because cisplatin, pemetrexed, and radiation have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with cisplatin and pemetrexed, breastfeeding is not allowed during the course of the study. These potential risks may also apply to other agents used in this study. Female patients must have a negative pregnancy test (B-HCG test in urine or serum) prior to commencing study treatment.

3.2.10 Patients unable to comply with the protocol

3.2.11 Known active hepatitis B infection, active hepatitis C infection or known HIV carrier

3.2.12 Known or suspected active drug or alcohol use

3.2.13 Known hypersensitivity to afatinib, cisplatin, or pemetrexed

3.2.14 Concomitant treatment with strong inhibitor of P-gp (see Section 5.5 for restrictions)

3.2.15 Individuals with a history of an active malignancy (other than the current lung cancer diagnosis) within the last 3 years (except non-melanoma skin cancer or a non-invasive/*in situ* cancer).

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

We do not expect that the inclusion or exclusion criteria will impact the enrollment of women, minorities, or other underrepresented populations as lung cancer affects people of all genders, races, and socioeconomic classes.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

   Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

5. TREATMENT PLAN

Treatment will be divided into 5 stages:

1) Induction, consisting of afatinib for two 4-week cycles;
2) Concurrent chemotherapy and radiation, 4D conformal radiation therapy with cisplatin/pemetrexed for two 3-week cycles if surgery is planned and for up to four 3-week cycles if surgery is not planned ;
3) Surgical resection for those who are deemed to be a surgical candidate;
4) Adjuvant chemotherapy (optional), for those who underwent surgery up to two additional 3-week cycles of chemotherapy may be given post-operatively
5) Consolidation with afatinib for twenty-six 4-week cycles (2 years). Only those patients who had a partial or complete response or tumor shrinkage including 0% change on RECIST to 2 cycles of induction afatinib according to RECIST criteria will be eligible to receive consolidation afatinib. While any patient with RECIST growth of 1% or more is not eligible.

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for afatinib, cisplatin, and pemetrexed are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Treatment Description					
Agent	**Pre-medications[a]; Precautions**	**Dose**	**Route[a]**	**Schedule**	**Cycle Length**
Afatinib	Take on an empty stomach (at least one hour before and at least three hours after food intake)	40mg	PO	During Induction: Daily for 8 weeks (2 cycles) During Consolidation[b]: Daily for 2 years (26 cycles)	4 weeks
Cisplatin	Use institutional guidelines, or: 1) Ondansetron 16 mg po/IV on Day of infusion, then 8 mg PO bid x 3 days starting Day after cisplatin 2) Aprepitant 125 mg po Day 1, 80 mg po for Day 2 and 3 3) Mannitol 25% 12.5 GM IV x 1 4) Dexamethasone 12 mg PO/IV on Day of infusion 5) Pre-hydration: 1 liter NS with 20 mEq/L potassium chloride + 2 gm/L magnesium sulfate 6) Post-hydration: 1 L NS	75 mg/m^2	Use institutional guidelines	During Concurrent Chemotherapy and Radiation and/or during Adjuvant Chemotherapy: Day 1 of Cycles 1-4[c]	3 weeks

Treatment Description					
Agent	**Pre-medications[a]; Precautions**	**Dose**	**Route[a]**	**Schedule**	**Cycle Length**
Pemetrexed	Use institutional guidelines, or: 1) IM injection of 1000 mcg vitamin B12 (cyanocobalmin) given ≥ 5 days before Day 1 of Cycle 1 and approximately every 9 weeks while receiving pemetrexed and continuing until 3 weeks after the final dose. 2) Continuous folic acid supplementation with at least 400 mcg daily starting ≥ 5 days before Day 1 of Cycle 1 and continuing for 3 weeks after the final dose 3) Dexamethasone 4 mg po/IV BID x 5 days starting Day -1	500 mg/m^2 in 100 ml NS	Use institutional guidelines	During Concurrent Chemotherapy and Radiation and/or during Adjuvant Chemotherapy: Day 1 of Cycles 1-4[c]	3 weeks
Radiation therapy	Supportive care per routine clinical practice.	45-72 Gy[d]	External Beam	During Concurrent Chemotherapy and Radiation: Daily M-F starting at approximately Cycle 1 Day 1 (for practical purposes RT may begin +/- 3 weekdays from chemo Day 1)	N/A

a. Premedications for cisplatin and pemetrexed are suggestions. Medications may be given per institutional standards using standard infusion times,premedications, order of administration, etc. for each agent.
b. Only patients who had tumor shrinkage including 0% change per RECIST or a response to induction afatinib will receive consolidation afatinib as described above.
c. Cisplatin and pemetrexed will be given for two 3-week cycles with radiation if surgery is planned and for up to four 3-week cycles with radiation if surgery is not planned. Cisplatin and pemetrexed will be given for up to two 3-week cycles in the adjuvant (post-operative) setting (optional) for those who underwent surgery. If given, adjuvant chemotherapy should begin after sufficient recovery from surgery , typically within 8 weeks.
d. Patients who are considered operable will receive 2 cycles of preoperative chemotherapy with radiation therapy to 45-54 Gy. Surgery should be scheduled approximately 4-6 weeks following the completion of chemotherapy and radiation. Inoperable patients will receive 2 cycles of chemotherapy with radiation therapy up to 72 Gy.

5.1 Study Assessments

Note: A window of +/- 3 days can be applied to scheduled visits if necessary for holidays, vacations, inclement weather, etc.

5.1.1 Screening Evaluation

Scans must be done (28 days) prior to the start of protocol therapy; all other evaluations must be completed within 14 days prior to enrollment unless noted.

1) History and physical examination
2) Measurement of height, weight and vital signs (including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature).
3) Performance status evaluation
4) CBC with differential, basic metabolic panel (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium), magnesium, liver function tests (albumin, total protein, alkaline phosphatase, total and direct bilirubin, ALT, AST).
5) PET/CT scan of whole body to rule out metastatic disease
6) Brain MRI or CT (preferably with contrast unless contraindicated)
7) 12-lead electrocardiogram
8) PFTs including DLCO measurement (unless available from within 6 months of study enrollment)
9) Assessment of surgical operability by a thoracic surgeon with determination of one of the following: (does not have to be within 7 days from enrollment)
   a) resectable after induction therapy
   b) unresectable
   c) medically inoperable
   d) unable to make determination
10) Pregnancy test for women of childbearing potential. Sexually active women of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

5.1.2 Cycle 1 of Induction afatinib, Days 1 and 8

Screening labs and procedures may substitute for those on Cycle 1 Day 1 if performed within 3 days of Cycle 1 Day 1.

1) Interim history and physical exam
2) Measurement of weight and vital signs
3) Performance status evaluation
4) CBC with differential, basic metabolic panel, magnesium, liver function tests

5.1.3 Cycle 2 of Induction afatinib, Day 1

1) Interim history and physical exam
2) Measurement of weight and vital signs
3) Performance status evaluation
4) CBC with differential, basic metabolic panel, magnesium, liver function tests

5.1.4 After completion of Cycle 2 of Induction afatinib

1) CT of the chest for restaging and radiation planning (neck CT may be needed depending upon disease extent).
2) A PET scan should also be performed to further evaluate response to induction therapy. For participant convenience, these tests may be combined into one study (i.e. PET/CT of the chest and potentially the neck). If an individual patient is unable to undergo the PET scan, exceptions may be granted after discussion with the PI.
3) Administer Vitamin B12 1000 mcg IM (must be ≥ 5 days before Cycle 1 Day 1 of Chemotherapy/radiation and can be given before the end of induction afatinib if desired).
4) Prescribe folic acid at least 400mcg PO daily (must start ≥ 5 days before Cycle 1 Day 1 of Chemotherapy/radiation and can be given before the end of induction afatinib if desired).
4) Although the time required for radiation planning may vary, chemotherapy must start at least one week and no more more than 3 weeks after induction afatinib is completed. Radiation should start within 3 weekdays of chemotherapy.

5.1.5 Concurrent Chemotherapy/radiation.

1) Chemotherapy can be given for up to 4 cycles total but if surgery is planned, only 2 cycles should be given pre-operatively
2) If surgery is planned, the maximum pre-operative radiation dose is 54 Gy. If surgery is not planned, the dose of definitive radiation should be between 59.4 and 72 Gy.
3) Patients should be seen weekly throughout the duration of the radiation therapy. If radiation is complete but chemotherapy continues, patients should be seen at a minimum on Day 1 of each cycle. At each visit they should undergo:
    a. Interim history and physical exam
    b. Measurement of weight and vital signs
    c. Performance status evaluation
    d. CBC with differential, basic metabolic panel, magnesium, liver function tests

5.1.6 If applicable, surgery is expected to occur between 4 and 8 weeks after the completion of pre-operative radiation but the exact timing will be dependent upon patient recovery from concurrent chemotherapy and radiation and it will not be a deviation if surgery occurs outside this window. If the patient is unable to have surgery, they should receive definitive radiation therapy to a dose of 59.4-72 Gy. Most surgeons will request restaging CT scans and/or brain MRI prior to surgery but this is at the discretion of the treating physicians and is not required.

5.1.7 Between 6 and 10 weeks after surgical resection or completion of definitive radiation therapy, patients should have

1) Interim history and physical exam
2) Measurement of weight and vital signs
3) Performance status evaluation
4) CBC with differential, basic metabolic panel, magnesium, liver function tests
5) CT scan of the chest

5.1.8 Cycle 3 and 4 of Adjuvant Chemotherapy, Day 1

Note: This portion of therapy is optional, is intended only for patients who have completed surgical resection and may be omitted at the discretion of the treating physician. If patient will receive Adjuvant Chemotherapy, Cycle 3 will begin after adequate recovery from surgery at the discretion of the treating physician, no less than 6 weeks and no greater than 12 weeks after resection

1) Interim history and physical exam
2) Measurement of weight and vital signs
3) Performance status evaluation
4) CBC with differential, basic metabolic panel, magnesium, liver function tests

5.1.9 Consolidation afatinib:
Cycles 1-4, Day 1 of each cycle; Cycles 5-26, Day 1 of every 3rd cycle (Cycles 7, 10, 13, 16, 19, 22, and 25).
Note: Only those patients who achieved tumor shrinkage including 0% per RECIST, a partial response, or a complete response by RECIST to induction afatinib will proceed with consolidation afatinib. See section 5.1.11 for follow-up study assessments for those who are not receiving consolidation afatinib.
For patients who received Adjuvant Chemotherapy: Cycle 1 Day 1 consolidation afatinib must be no less than 3 weeks and no greater than 8 weeks after the last dose of chemotherapy.
For those who did not receive Adjuvant Therapy: Cycle 1 Day 1 must be no less than 6 weeks and no greater than 12 weeks after surgical resection or completion of definitive radiation therapy.

1) Interim history and physical exam
2) Measurement of weight and vital signs
3) Performance status evaluation
4) CBC with differential, basic metabolic panel, magnesium, liver function tests
5) CT scan of the chest will occur during consolidation afatinib q3 mo for 1 year, then q6 mo for 1 year. This means scans will occur prior to Cycle 1, 4, 7, 10,

13, 19, and 25. If a patient did not receive adjuvant chemotherapy, the CT scan obtained 6-10 weeks after surgery or definitive chemoradiation can be considered their prior to cycle 1 of consolidation afatinib scan and this does not need to be repeated. If a patient did receive adjuvant chemotherapy, a new baseline CT scan should be obtained prior to consolidation afatinib If a patient discontinues consolidation afatinib before their prescribed 2 years is complete, they should still follow the same surveillance CT schedule as if they were still on drug

5.1.10 For patients not receiving Consolidation afatinib: Surveillance with the following assessments is every 3 months +/- 1 week for 2 years (starting from the last treatment date). This is to ensure that patients have the same follow-up frequency whether or not they are on afatinib. Note CT scan is not required at every 3 months, see below.

1) Interim history and physical exam
2) Measurement of weight and vital signs
3) Performance status evaluation
4) CBC with differential, basic metabolic panel, magnesium, liver function tests
5) The schedule of CT scans after completion of chemotherapy, radiation and potentially surgery is every 3 months during the first year, every 6 months during years 2 and 3, and once during year 4. After the completion of the 4th year, follow-up is at the discretion of the treating doctor.

5.1.11 End of Treatment Visit

To be completed 20 to 30 days after the final dose of study drug is administered
1) Interim history and physical exam
2) Measurement of weight and vital signs
3) Performance status evaluation
4) CBC with differential, basic metabolic panel, magnesium, liver function tests

5.1.12 Post Treatment Follow-up
1) Chest CT scans should be continued after consolidation afatinib (or after the period of prescribed consolidation afatinib if discontinued early) as follows – every 6 months during the 3rd year and once per year during the 4th year. As in 5.1.10, for those who were not eligible to receive consolidation afatinib, the schedule of CT scans after completion of chemotherapy, radiation and potentially surgery is every 3 months during the first year, every 6 months during years 2 and 3, and once during year 4. After the completion of the 4th year, follow-up is at the discretion of the treating doctor.

5.2 Agent Administration

5.2.1 Afatinib (also may be referenced as BIBW 2992)

For administrative purposes treatment will be divided into treatment cycles, which are each 4 weeks (28 days) in duration. Patients will take a single oral dose of 40 mg afatinib each day. The medication should be taken at the same time each Day (±2 hours) on an empty stomach, which is defined as at least one hour before food intake and at least three hours after food intake.

The tablet should be swallowed with a glass of water. Afatinib tablets are film-coated and therefore should not be chewed or crushed. If patients are truly unable to swallow the tablets after an effort to conform to the protocol (such as those with severe dysphagia or odynophagia or those dependent on a gastric tube for feeding), the study drug may be dissolved and swallowed after dispersing the afatinib tablets according to the following procedure: Place the tablet into a glass containing 50 mL isotonic sodium chloride solution. Stir until the tablet is broken up into very fine particles (about 15 minutes). Drink the suspension immediately or administer via a gastric tube if applicable. Rinse the glass with another 50 ml of isotonic sodium chloride solution and drink or administer the supplementary solution via the gastric-tube again (to pick up any drug remaining in the glass/gastric-tube). Isotonic sodium chloride must be prescribed by the investigator if this protocol is to be used.

If a patient inadvertently does not take afatinib 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. 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. If a dose is vomited within 1 hour of administration, medications to control nausea and vomiting should be used, and the dose can be repeated. Patients should report all vomited, missed or delayed doses to the study staff and will be provided with a medication diary which should be turned in at every visit.

See table above for dosing information.

5.2.2 Cisplatin

Administration
Cisplatin should be prepared and administered as per institutional guidelines.

Dosing
See table, section 5 above.

Hydration
Pretreatment hydration as per institutional guidelines is recommended.

Observation period
Patients receiving cisplatin should be observed carefully for possible anaphylactic- like reactions and supportive equipment and medication should be available to treat such a complication.

Vital Signs
Should be checked prior to administration of cisplatin and as needed during and after infusion.

Infusion reactions
Anaphylactic-like reactions have been occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration.

Grade 1: Slow the infusion until symptoms resolve, then restart the infusion at the initial planned rate

Grade 2: Stop the infusion. Administer H1 and/or H2 blockers +/- dexamethasone, according to physician discretion/institutional guidelines. Restart cisplatin when symptoms resolve and pretreat before subsequent doses of cisplatin.

Grade 3/4: Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines. Patient should be removed from protocol therapy.

5.2.3 Pemetrexed

Administration
Pemetrexed should be prepared and administered as per institutional guidelines

Dosing
See table above.

Observation period
Patients should be observed for infusion reactions when receiving pemetrexed

Vital Signs
Vital signs should be checked before administration of pemetrexed and as indicated by clinical change thereafter

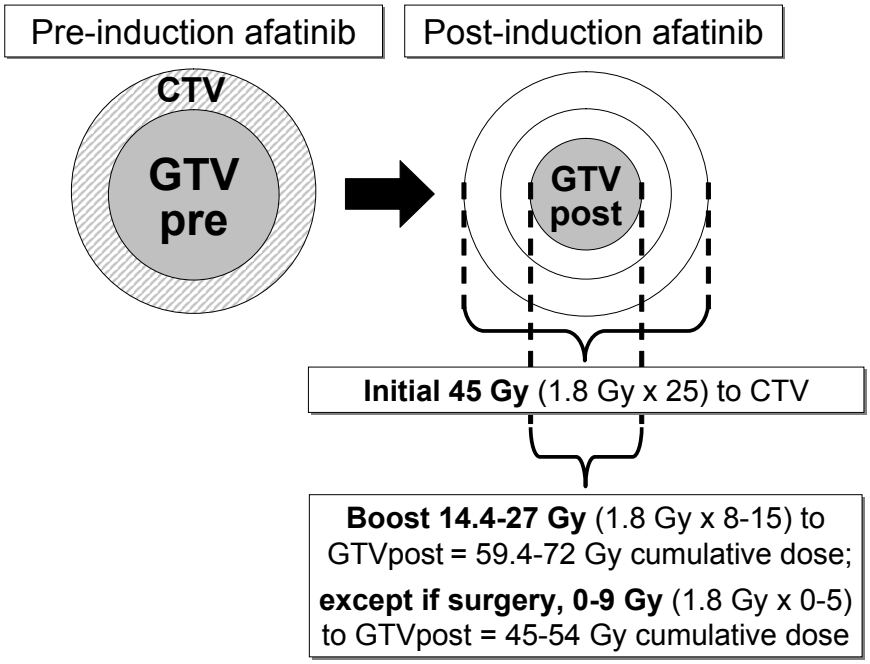
Infusion reactions
Infusion reactions are infrequent with pemetrexed. If an allergic/hypersensitivity reaction occurs, please follow guidelines under “Cisplatin” section above.

5.3 Radiation Therapy

5.3.1 Overview - Radiation Schema

For every participant enrolled onto the trial, 4D CT-based treatment planning must be performed and a conformal radiation plan up to a dose between 63 Gy and 72 Gy at 1.8 Gy per fraction over 35-40 fractions (7-8 weeks) must be designed prior to radiation treatment start. The rationale for designing a complete radiation plan to 59.4-72 Gy even for patients who are intended to undergo surgery is to avoid any radiation treatment interruptions in case a patient turns out not to be eligible for surgery.

Radiation will initially encompass the pre-induction gross tumor volume (GTVpre) and an area of presumed microscopic spread, i.e., clinical target volume (CTV), to 45 Gy. A radiation boost will be given to the post-afatinib gross tumor volume (GTVpost), with the total dose being individualized and limited by carefully defined normal tissue constraints (see Table 5.1). An overview is given below:



5.3.2 Simulation

All simulations will be done on CT scanners capable of acquiring 4D CT image data sets. The imaging session will consist of acquisition of a free-breathing treatment planning CT image data set and a 4D CT image data set consisting of 0% to 90% phase CT sets representative of a single respiratory cycle, as per individual institutional practice. CT images should be acquired with the application of intravenous contrast, unless medically contraindicated. Omission of intravenous contrast for non-medical reasons is discouraged but permissible if a diagnostic chest CT scan with iv contrast that is not older than 4 weeks is available to guide the delineation of mediastinal target volume and critical normal tissue structures. Oral esophageal contrast is optional. The slice thickness through tumor-

containing regions should be 3 mm or less. Custom patient immobilization is not required but strongly encouraged. Fusion with pre-afatinib induction PET/CT as well as post-afatinib induction PET images is recommended though not mandatory to allow definition of target volumes. Repeat 4D CT scanning during the treatment course to take advantage of tumor regression or adjust for changes in atelectasis or pleural effusion for replanning purposes is allowed.

5.3.3 Tumor target volumes

Visible gross tumor should be outlined on each CT slice. For the identification of parenchymal lung tumor, lung windows should be used. For the identification of tumor in the mediastinum including lymph nodes, an appropriate soft tissue window should be used. Interpolation is allowed. The use of the average intensity projection of the 4D CT data set as reference scan is recommended.

For the purpose of this protocol, the following target volumes are defined:

GTV Gross tumor volume is all known gross disease visible on the 50% (exhale) phase of the 4D planning CT as well as pre-afatinib induction CT and modified as necessary based on PET images. Mediastinal lymph nodes are considered involved if they are FDG-avid on PET or biopsy-proven (for example, on mediastinoscopy). Suspicious lymph nodes that are PET negative may also be included at the treating physician's discretion, for example if they are > 1 cm in short axis diameter, lie in a predicted path of lymphatic spread, or have a necrotic center.

GTVpost denotes visible gross tumor on the 50% phase planning CT, in conjunction with the post-afatinib induction PET scan for radiation planning.

GTVpre denotes visible gross tumor on the most recent pre-afatinib induction CT scan, in conjunction with the pre-treatment PET. It is recommended that this volume be defined on the planning CT scan by fusion with the pre-afatinib induction PET/CT. The purpose of outlining the GTVpre is to guide the definition of the CTV (see below), which will receive 45 Gy.

The GTV may be divided into two separate volumes for primary tumor (GTV-p) and involved nodal groups (GTV-n) at the treating physician's condition.

ITV For the purpose of this protocol, the **ITVpost** will be defined as GTVpost plus internal margin for respiratory tumor motion.

The ITVpost may be separated into ITV-p (for primary tumor) and ITV-n (for involved lymph nodes) as per institutional practice.

Generation of the ITVpost may involve the reconstruction of a Maximum Intensity Projection (MIP) of the 4D CT image data set, which will be used for outlining the GTV. MIP represents an algorithm that analyzes the maximum intensity at each point across all 10 phase CTs. The resultant composite CT essentially shows a 4D representation of the tumor location over the entire respiratory cycle, which works best for tumors confined to the lung parenchyma. The delineated MIP-GTVs should be validated against the position of the GTVs on

each of the 10 phase sets, either by individual comparisons or overlaying the MIP volumes on a movie loop displaying the 4D CT data (51).

The ITVpost may also be constructed using other approaches as per institutional practice, for example by contouring the GTV volumes on the inhale, exhale, and free breathing sets, followed by interpolation or fusion of the volumes.

CTV The clinical target volume includes:
1) The pre-afatinib induction ITV (ITVpre), and
2) An automatic 5- to 10-mm margin around the ITVpre for microextension of tumor as clinically indicated.
The CTV should be extended manually to account for presumed respiratory motion of the ITVpre, based on the extent of motion that is estimated for the ITVpost on the 4D planning CT. The CTV must always encompass the ITVpost.
The CTV around the gross primary tumor may be extended beyond the automatic margin at the individual physician's discretion, for example to include atelectasis/postobstructive changes.
The CTV may also be extended at the individual physician's discretion to cover likely lymphatic drainage routes. However, comprehensive ENI is not allowed and careful consideration must be given to any increase in lung V5 or V20 that may result from an increase in the CTV volume, thereby limiting the maximum achievable dose to the gross tumor.
The CTV may be manually constricted if it extends into normal tissue structures that do not contain microscopic spread (such as lumen of a vessel, vertebral body, or esophagus).

PTV The planning target volume entails a margin that accounts for variations in treatment delivery, including variations in setup between treatments. The PTV should be at least 5 mm, but no more than 10 mm, taking into account the specifics of each case. There will be two PTV volumes: **PTV1 (initial)** = CTV plus 5-10 mm margin, **PTV2 (boost)** = ITVpost plus 5-10 mm margin. Manual editing of PTV2 is allowed if this minimizes overlap with critical normal tissue structures such as the esophagus. Additional PTVs may be generated if additional conedowns are to be performed. Treating PTV1 to full dose without a conedown is acceptable if there was less than a complete response after afatinib and as long as organ at risk constraints are not exceeded (see also 5.3.4 below).

5.3.4 Dose prescription

- The daily fraction size for all treatments will be 1.8 Gy.
- PTV1 should be carried to 45 Gy, but a lower dose of at least 39.6 Gy is acceptable if needed to meet normal tissue constraints (see Table 5.1).
- For participants who are not surgical candidates, the PTV2 will be boosted with 14.4-27 Gy to bring the total cumulative dose to at least 59.4 Gy but no more than 72 Gy at the treating physician's discretion. If PTV1 was treated to less than 45 Gy, a higher boost dose is allowed, as long as the cumulative dose does not exceed 72 Gy.
  Because the effectiveness of radiation is to a great extent dependent on tumor size (50), higher doses should be used for larger tumor sizes. The following guidelines are recommended for individualized treatment of gross tumor post-afatinib induction (cumulative doses):
  - Complete Response: 59.4-63 Gy
  - Tumor diameter < 3 cm: 63-66.6 Gy
  - Tumor diameter > 3 cm: 70.2-72 Gy

  However, irrespective of tumor size, the normal tissue constraints specified in Section 5.3.6 must not be exceeded.
- For participants who are deemed surgical candidates, the PTV2 will be boosted with up to 9 Gy to bring the cumulative dose to up to 54 Gy. If PTV1 was treated to less than 45 Gy, a higher boost dose is allowed, as long as the cumulative dose does not exceed 54 Gy.
  The following guidelines are recommended for individualized treatment of gross tumor post-afatinib induction in patients that will undergo surgery (cumulative doses):
  - Radiographic Complete Response (CR): 45 Gy
  - Radiographic partial response or no response: 50.4-54 Gy
- If there is no CR after afatinib induction, it is allowed to boost the initial target volume (PTV1) to full dose as long as the pre-specified normal tissue constraints in Section 5.3.6 are not violated.
- In the cumulative plan, 100% of the ITVpost volumes should be covered by 100% of the prescribed dose, but coverage with ≥ 95% of the prescribed dose will be acceptable if 100% cannot be reached.
- In the cumulative plan, 100% of each PTV volume should be covered with at least 95% of the prescription dose. If this coverage cannot be achieved, it is acceptable though not desirable to cover ≥ 95% of each PTV with ≥ 95% of the prescription dose. Minimum covering dose should be 90% of prescription dose for 99% of the PTV.
- Hotspots inside and outside the PTV should be limited to 110% of the prescribed dose.

5.3.5 Technical Factors

- Highly conformal radiation plans must be developed for all participants, and both conventional forward planning and IMRT are allowed. For conventional planning, the use of simple opposed beam arrangements is discouraged unless required to meet lung DVH constraints. Beam arrangements should utilize 3-4 fields for the initial and boost phases to improve dose conformality. Photon energies of 6-18 MV are permissible. Preference to IMRT should be given in cases where dose of > 66.6 Gy are deemed necessary and where normal tissue constraints are difficult to meet with conventional beam arrangements. IMRT planning should utilize 6 MV photons and typically no more than 5 beams in order to minimize low dose lung exposure.
- Heterogeneity corrections must be done for all patients.
- In patients where respiratory peak-to-peak motion of the tumor exceeds 2.0 cm or if needed to meet lung DVH constraints, respiratory gating is permissible and will be performed according to institutional practice.

5.3.6 Normal Tissue Structures and Dose Constraints:

- It is recommended that normal tissue structures be drawn on the average intensity projection but use of the free breathing helical CT scan or a 4D phase CT series at mid-expiration such as the 30% phase according to institutional practice is acceptable. Significant variations in lung volume between these different CT series are not expected. Autosegmentation or interpolation may be used.
- It is recommended that radiation dosimetry be done on the average intensity projection set but use of the free breathing helical CT scan or a 4D phase CT series at mid-expiration such as the 30% phase according to institutional practice is acceptable.
- The following structures must be generated, except were indicated:
  Right Lung and **Left Lung**
  Combined Lungs and **Combined Lungs minus ITVpost**
  Spinal Cord (thoracic) and **Spinal Cord with 5 mm safety margin** (to account for set-up uncertainty)
  Esophagus (entire length)
  Heart (for the purpose of this protocol, contour the pericardial sac from the apex of the heart to a level of ~1 cm inferior to the PA bifurcation)
  Left Ventricle (optional)
  Ipsilateral Brachial Plexus (for tumors/mediastinal nodes with epicenter above aortic arch)
  Liver (for tumors near the diaphragm)

Table 5.1. Organs at risk (OAR) and dose constraints for definitive radiation plans to 59.4-72 Gy

STRUCTURE	CONSTRAINTS	DEVIATIONS

Combined lungs minus ITV	V5 ≤ 65% V20 ≤ 35% MLD ≤ 20 Gy	V20 = 36-40% and/or MLD ≤ 22 Gy acceptable as a minor deviation in patients with excellent pulmonary function.
Comments: (1) If using IMRT, it is strongly advised to ***minimize the volume of lung receiving 5 Gy or more***, i.e., attempt a V5=45% or even less. (2) If a patient is likely to undergo surgery, special care should be taken to minimize beam exit/entrance through the *contralateral* lung (V5 for contralateral lung < 25% is recommended).		
Spinal cord	max 45 Gy	A maximum dose of 50 Gy is acceptable to achieve lung sparing and/or if there is tumor in a para-spinal location.
Spinal cord with 5 mm margin	V45 ≤ 1%	The V45 constraint may only be exceeded in cases where gross tumor is in close vicinity of the spinal cord; however, daily preportal imaging will be required to ensure precise set-up to avoid that high dose isodose line shift near or onto the spinal cord.
Comments: The rationale for placing a 5 mm margin around this structure is that radiation induced transverse myelitis is an unacceptable complication and must be avoided. Without a margin, isodose lines of > 45-50 Gy could end up in close proximity of the cord, which may lead to cord overdosing due to patient set-up uncertainty and variation during the course of treatment. The maximum allowed dose is 50 Gy defined as the smallest volume in the radiation planning system receiving this dose (typically a single voxel).		
Esophagus	V50 ≤ 40% V60 ≤ 30% max 70 Gy	No deviations permitted
Comments: No DVH constraints for esophagitis have been firmly established in the literature. It is strongly advised to keep the V50 and V60 values as low as possible and not place hotspots onto or near the esophagus. The maximum allowed dose is 70 Gy, defined as the smallest volume in the radiation planning system receiving this dose (typically a single voxel), but ***limiting the maximum dose to 63-66 Gy*** is recommended to further reduce the risk of severe esophagitis. The tumor PTV may be modified manually as needed to meet the constraints.		
Heart	V40 ≤ 40% V60 ≤ 30% max 70 Gy	No deviations permitted
Comments: No DVH constraints for the heart have been firmly established in the literature. For the purpose of this protocol, it is strongly advised to keep the V60 and maximum dose to any heart volume as low as possible. Hotspots in the heart should be avoided.		
Left ventricle (optional)	V40 ≤ 10% V50 ≤ 1%	Guideline only
Comments: No DVH constraints for the left ventricle have been firmly established in the literature. For the purpose of this protocol, it is strongly advised to keep the maximum dose to any ventricle volume as low as possible. Hotspots in the heart should be avoided.		
Brachial plexus	max 60 Gy	Maximum dose between 60 and 66 Gy will be considered a minor deviation (for patients with apical tumors or supraclavicular lymphadenopathy)
Liver	V30 ≤ 30%	No deviations permitted

MLD,
mean lung dose; max, maximum dose

5.4 Surgery

5.4.1 Surgical Candidacy

- All patients must be evaluated by medical oncologist, radiation oncologist, and thoracic surgeon prior to enrollment to study.
- All patients require a mediastinoscopy or other appropriate procedure such as thoracoscopy, endoscopic ultrasound guided biopsy or supraclavicular biopsy, to assess the status of mediastinal lymph node involvement or the highest level of suspected involved nodes, prior to protocol enrollment.
- Surgical resectability and operability must be documented by a thoracic surgeon as a baseline evaluation.

5.4.2 Timing and Type of Surgery

- Surgery should be scheduled approximately 4-8 weeks following the completion of chemoradiation therapy.
- Patients may undergo a lobectomy or pneumonectomy at the discretion of the treating thoracic surgeon. Sub-lobar resections are not recommended.
- At the time of surgical resection, all visible and technically accessible bronchopulmonary, hilar, and mediastinal lymph nodes should be removed and submitted, appropriately labeled, to the pathologist.
- Surgical Adverse Events: All acute and late adverse events from protocol surgery will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

5.5 General Concomitant Medication, Supportive Care Guidelines, and Management of Adverse Events

Afatinib is a substrate of P-gp and its plasma concentrations can be affected by the use of P-gp inhibitors (data on file) and it is also likely that P-gp inducers could also influence afatinib plasma concentrations. The use of potent P-gp inhibitors (including Cyclosporin, Erythromycin, Ketoconazole, Itraconazole, Quinidine, Phenobarbital salt with Quinidine, Ritonavir, Valspodar, Verapamil) and potent P-gp inducers (including St John's wort, rifampicin) has to be avoided during treatment with afatinib.

G-CSF-based growth factors (Neupogen, Neulasta) are not recommended during the course of radiation therapy, except in the case of life-threatening febrile neutropenia (52).

Erythropoietin-stimulating agonists (Aranesp, Procrit, Epogen) are not recommended for the treatment of anemia. Blood transfusions are encouraged for treatment of anemia.

Supportive care medications for patients receiving chemotherapy and radiation treatment should be given as per standard practice.

5.5.1 Management of diarrhea following treatment with afatinib

Close monitoring and proactive management of diarrhea is essential for successful treatment of patients with afatinib. Early and appropriate intervention can prevent the development of more severe diarrhea. In most cases, loperamide controls diarrhea caused by afatinib. Loperamide should be available at the start of therapy and kept with the patient at all times; it is therefore advisable that patients be given a prescription at the time of initiating treatment with afatinib.

The recommendations for management are as follows:

- If any diarrhea is experienced (CTCAE Grade 1), two 2 mg loperamide tablets (total 4 mg) should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 8 tablets (16 mg).
- In the event of diarrhea patients should be advised to avoid lactose-containing products or any food known to aggravate diarrhea
- Other anti-diarrheal medications that could be used include diphenoxylate/atropine (Lomotil, 5 mg, four times a day), tincture of opium (15-20 drops orally every 4 hours) or octreotide (150 to 300 mg SQ twice a day).
- Oral hydration is essential regardless of severity of diarrhea; appropriate rehydration (1.5 L/m^2/Day plus equivalent of actual fluid loss) and electrolyte replacement has to be ensured in the event of CTCAE Grade 2 and Grade 3 diarrhea.
- For CTCAE Grade 3 diarrhea or CTCAE Grade 2 diarrhea lasting ≥ 2 days (48 hours) despite adequate antidiarrheal treatment, afatinib must be paused until recovery to CTCAE ≤ Grade 1. Upon recovery, afatinib should be resumed at a reduced dose according to the dose reduction scheme outlined in Section 6.3.1.
- If despite optimal supportive care and a treatment pause, diarrhea does not resolve to CTC Grade ≤1 within 14 days, the patient must not receive any further afatinib treatment.

5.5.2 Management of nausea and vomiting following treatment with afatinib

Nausea and vomiting may significantly affect patients' adherence to the treatment and their quality of life. In order to reduce the occurrence and the intensity of emesis, the patients should be treated with an aggressive antiemetic program such as the following:

CTCAE Grade	Antiemetic treatment
Nausea = grade 0 and Vomiting = grade 0	No antiemetic prophylactic treatment
Nausea = grade 1 and Vomiting = grade 0	No antiemetic treatment
Nausea = grade 2 and Vomiting = grade 0 Nausea = grade 0, 1 or 2 and Vomiting = grade 1 or 2	Antiemetic treatment[1] Pause afatinib treatment if grade 2 vomiting or grade 2 nausea persist for 7 or more consecutive days despite optimal supportive care. Resume treatment when CTCAE grade ≤ 1.
Vomiting ≥ grade 3 or Nausea ≥ grade 3	Antiemetic treatment[1] Pause afatinib treatment until return to CTCAE grade ≤ 1 or baseline[2].

1 Antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference

2 Baseline is defined as the CTCAE grade at the start of treatment

After a treatment pause the dose of afatinib should be reduced according to the dose reduction scheme table. If patient has not recovered to CTCAE Grade ≤ 1 or baseline within 14 days study treatment should be permanently discontinued.

In case of nausea and/or vomiting ≥ CTCAE grade 2, appropriate hydration (1.5 L/m2/Day plus hydration deficit) must be ensured.

5.5.3 Management of rash following treatment with afatinib

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and reduce the rash.

The recommendations for management are as follows:

- General/Prevention: strict sun protection; use of a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide; use of a thick, alcohol-free emollient cream; avoid harsh detergents, avoid using a solarium.
- CTCAE Grade 1 rash: mild rash may not need treatment. However, if treatment is considered necessary, moisturizing lotions, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel can be used.
- CTCAE Grade 2 rash: relief from major symptoms caused by CTCAE Grade 2 skin related adverse events should be achieved by a combination of local and systemic therapies including:
    1) Systemic antibiotics (doxycycline or minocycline etc.).
    2) Topical treatment (hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream).

And / or
1) Antihistamines (diphenhydramine, etc.)
2) Oral prednisone (short term i.e., < 14 days treatment) may be added at investigator's discretion.

Systemic and topical treatment should be initiated at the start of CTCAE Grade 2 rash and continue until improvement or resolution to CTCAE Grade ≤1. If grade 2 rash persists for ≥14 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment for up to 14 days followed by a reduction in the dose of afatinib.

- CTCAE Grade 3 (or greater) rash: may be treated in a manner similar to CTCAE Grade 2 rash. In the event of CTCAE Grade ≥3 rash, treatment with afatinib should be held until recovery to CTCAE Grade ≤1. Treatment should be resumed at a reduced dose (see section 6.3.1). If CTCAE Grade ≥3 rash does not resolve to CTCAE Grade ≤1 within 14 days of stopping afatinib treatment and despite optimal supportive care, the patient should not receive any further treatment with afatinib.

5.5.4 Interstitial Lung Disease (ILD)
Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude ILD. Study drug should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug should be permanently discontinued and appropriate treatment instituted as necessary. Although there is no established treatment, systemic corticosteroids are often administered.

5.6 Contraception and Pregnancy

Female patients who are not of childbearing potential due to being postmenopausal (2 years without menses) or surgical sterilization (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception.

All other female patients are considered to have childbearing potential and should use adequate contraception throughout the study (from screening until end of study participation or 28 days after last dose of trial medication, whichever is later).

Acceptable methods of contraception for females include hormonal contraception and double barrier method. Double barrier method of contraception is defined as two barrier methods used simultaneously each time the patient has intercourse. Accepted barrier methods include diaphragm, female condom, cervical cap, male condom and IUD (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). If hormonal contraceptives are used, at least one barrier method should also be used. Partner vasectomy, natural 'rhythm' and spermicidal jelly/cream are not acceptable as methods of contraception.

Male patients should use adequate contraception throughout the study (e.g. condom and spermicidal jelly).

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must capture any drug exposure during pregnancy. The investigator will follow the pregnancy until outcome is known. A SAE report must be forwarded to the pharmaceutical company if the outcome of the pregnancy results in an abortion/miscarriage or the occurrence of any other SAE(s).

5.7 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue for the duration of Induction therapy (8 weeks), Chemotherapy and Radiation (6-8 weeks), Surgical resection (approximately 10 weeks including recovery time), Adjuvant therapy (6 weeks), and Consolidation therapy (2 years). Treatment may be stopped before this time if one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.8 Duration of Follow Up

Participants will be followed after removal from study for 5 years or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Surveillance CT scans to assess for recurrence are recommended every 3 months for the first year and then every 6 months for next 3 years, and then annually x 1 year, and then as needed, with consideration of a biopsy at the time of progression. Patients distant to the treatment center will be encouraged to follow up at the treating center, or send any follow up medical records and imaging studies on a three month basis.

5.9 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.6 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), Lecia Sequist at 617-724-4000.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc, see section 5.5).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

6.1.1 Afatinib

Please refer to the section "Listed Adverse Events" of the most recent version of the afatinib Investigator's Brochure for details.

6.1.2 Cisplatin

Known potential toxicities associated with cisplatin include myelosuppression, peripheral neuropathy, nausea/vomiting, nephrotoxicity, and allergic reaction. Please see the package insert for a comprehensive list of adverse events.

6.1.3 Pemetrexed

Known potential toxicities associated with pemetrexed include myelosuppresion, nausea/vomiting, rash, and allergic reaction. Please see the package insert for a comprehensive list of adverse events.

6.1.4 Adverse Event List for Radiation

>10%:
Fatigue
Mild to moderate rash
Mild to moderate esophagitis
Dry cough
Grade 1 (radiographic) or grade 2 pneumonitis

1-10%:
Moist desquamation of skin
Severe esophagitis
Severe pneumonitis
Dyspnea or hypoxia
Fracture (ribs, vertebral body)

<1% (Serious or life-threatening):
esophageal obstruction or perforation
fistula formation
severe hemoptysis
pneumonitis requiring ventilation
myocardial infarction
constrictive pericarditis
severe congestive heart failure
transverse myelitis
brachial plexopathy
skin ulceration
radiation-induced cancer

6.2 Toxicity Management

Toxicity management will be as per standard practice during chemotherapy and radiation therapy. In addition, please see Supportive Care Guidelines in section 5.5 and follow dose modifications and delays in section 6.3 as appropriate.

6.3 Dose Modifications/Delays

6.3.1 Afatinib Dose Modifications/Delays

In the event of treatment-related toxicities, the treatment with afatinib should be handled according to the schedule below. Note that if dose reduction of afatinib is required during Induction or Consolidation, no re-escalation is allowed in subsequent cycles. Please see section 5.5 for management of adverse events.

Dose Modifications/Delays in response to SAEs for Afatinib during Induction and Consolidation

AE type and grade	Action	Dose reduction scheme
Events related to study drug (except ILD and decreased LVEF which require special instructions below): • Any drug related AE CTCAE Grade ≥ 3 • CTCAE Grade ≥ 2 diarrhea persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrheal medication/hydration • CTCAE Grade ≥ 2 nausea and/or vomiting persisting for 7 or more consecutive days despite adequate anti-emetic treatment/hydration • CTCAE Grade ≥ 2 worsening renal function as measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate of more than 50% from baseline	Pause treatment with afatinib until patient has recovered to CTCAE Grade ≤ 1 or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to CTCAE Grade ≤ 1 or baseline within 14 days study treatment should be permanently discontinued[2].	If patient was receiving 40 mg, resume treatment at a dose of 30 mg. If patient was receiving 30 mg, resume treatment at a dose of 20 mg. If patient was receiving 20 mg, discontinue afatinib.

1. Baseline is defined as the CTCAE grade at the start of treatment
2 In the event that the patient is deriving obvious clinical benefit in the opinion of the investigator, but has not recovered within 14 days, the further treatment of the patient will be decided by the BI clinical monitor in agreement with the investigator.

Dose reductions should always follow a treatment pause. In the event of a treatment pause, subsequent visits/courses should not be delayed.

Special situations

Patients will discontinue treatment if they experience deterioration in left ventricular cardiac function (LVEF) to CTCAE Grade ≥ 3.

Patients will discontinue treatment if they are diagnosed with ILD.

In the event of a prolonged (≥ 7 consecutive days) Grade 2 drug-related event not listed in the table above, which is poorly tolerated by the patient, the investigator may choose to pause the medication for up to 14 days to allow the patient to recover to Grade 1 or baseline followed by a dose reduction according to the schedule in the table.

6.3.2 Cisplatin/Pemetrexed Dose Modifications/Delays

If dose reduction of agents is required during chemoradiation, no re-escalation is allowed in subsequent cycles during radiation therapy. However, cisplatin and pemetrexed may be restarted at dose level 0 after the completion of radiation therapy (i.e. during Adjuvant Therapy).

If all treatment (cisplatin, pemetrexed, and radiation) is interrupted for > 3 weeks continuously, the subject should be removed from the protocol. Otherwise, patients with partial treatment interruptions and dose reductions may continue treatment at the investigator's discretion.

Note that if a toxicity is felt to be more related to one chemotherapy drug than the another, the investigator may choose to dose reduce the culprit drug and leave the other drug at the previous dose level.

Dose Modifications for Cisplatin/Pemetrexed during Concurrent Chemoradiation and Adjuvant Therapy

Dose Level	Pemetrexed	Cisplatin
0	500 mg/m2	75 mg/m2
-1	400 mg/m2	50 mg/m2
-2C	Hold	50 mg/m2
-2P	500 mg/m2	Hold

-2C = cisplatin continuing, pemetrexed held
-2P = pemetrexed continuing, cisplatin held

Hematologic Toxicity

Dose delays on Day 1 of a new cycle of chemotherapy

ANC		Platelet	Cisplatin and Pemetrexed
≥ 1500/mcl	and	>100,000/mcl	Continue with previous dose
<1500/mcl but >500/mcl	or	<100,000/mcl	Hold*

*Check counts at least weekly and resume therapy at previous dose (no dose reduction) when counts recover to ANC > 1500 and platelets > 100,000/mcl. If, after 3 weeks of holding drugs ANC still < 1500 or platelet < 100,000, contact the Principal Investigator.

Hold both radiation therapy and chemotherapy for neutropenia (ANC<500 cells/mcl). Resume radiation when ANC ≥ 500 cells/mcl and resume chemotherapy when ANC ≥ 1500 cells/mcl with a dose reduction of cisplatin and pemetrexed to dose level -1.

Hold both radiation therapy and chemotherapy for febrile neutropenia (ANC < 1000 cells/mcl). Once afebrile ≥ 48 hours, resume radiation when ANC ≥ 1000 cells/mcl and resume chemotherapy when ANC ≥ 1500 cells/mcl with a dose reduction of cisplatin and pemetrexed to dose level -1. Febrile neutropenia occurring despite dose reduction during chemoradiation (for any AE) will result in discontinuation of the pemetrexed, but continuation of the cisplatin at the previous dose (-2C dose level).

Renal Toxicity:

Based on Day 1 of each cycle for cisplatin and pemetrexed:

Creatinine Clearance	Action
CrCl < 45 ml/min (see Appendix C)	Hold cisplatin and pemetrexed. Administer fluids and repeat creatinine clearance weekly.
CrCl ≥ 45 ml/min after 1st week	Administer cisplatin and pemetrexed at full dose
CrCl < 45 ml/min after 2nd week	Discontinue cisplatin therapy for all subsequent cycles. May skip cycle and administer pemetrexed in future cycles only if CrCl > 30 (-2P dose level).

Treatment-Induced Esophagitis

AE grade	Action
CTCAE Grade 3	Hold cisplatin and pemetrexed and institute supportive care measures. May hold radiation for up to 3 treatment days*. Re-evaluate patients one week later. Once improved to grade ≤ 2, resume pemetrexed and cisplatin with dose reduction to dose level -1.
CTCAE Grade 4	Hold radiation, cisplatin, and pemetrexed and institute supportive care measures. May hold radiation for up to 3 treatment days*. Monitor patients at least weekly. Once improved to grade ≤ 2, resume radiation, pemetrexed, cisplatin with dose reduction to dose level -1.

*If a treatment break of > 3 days is necessary, inform the Study PI.

Radiation Dermatitis

AE type grade	Action
CTCAE Grade 3 (moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion) in the radiation portals	Radiation may be held for up to 3 treatment days at the treating physician's discretion*.
CTCAE Grade 4 (necrosis, ulceration of dermis, spontaneous bleeding, skin graft indicated)	Hold radiation therapy and notify the Study PI

*Prolonged treatments breaks may be required as areas of moist desquamation may need 1 2 weeks or more to heal. For treatment breaks > 3 days, notify the Study PI.

Pulmonary Toxicity

Treatment-associated pneumonitis may develop in patients receiving chest radiation and chemotherapy but this is typically observed only after completion of radiation (3-6 months after treatment).

In the event of acute onset or worsening of pulmonary symptoms, hold radiation, pemetrexed, and cisplatin while the symptoms are evaluated. Consider performing a CT scan to evaluate for pulmonary embolus or infection as well as referral to a pulmonologist and consideration of bronchoscopy as clinically indicated. If a diagnosis of interstitial lung disease or pneumonitis cannot be made and symptoms improve, the patient may continue treatment. If pulmonary symptoms are judged to be treatment-related, all treatment (cisplatin, pemetrexed, and radiation) must be stopped.

Other

For all other treatment-related toxicities ≥ Grade 3, hold pemetrexed and cisplatin until the toxicities have resolved to ≤ Grade 2, then resume pemetrexed and cisplatin. At the investigator's discretion, pemetrexed and cisplatin may be continued at full dose or with one dose level reduction.

7. DRUG FORMULATION AND ADMINISTRATION

7.1.1 Afatinib

7.1.2 Description

Afatinib is a highly selective and potent low molecular weight, irreversible inhibitor of the erbB-family of tyrosine kinase receptors EGFR (erbB1 / HER1) and HER 2 (erbB2). The potency of afatinib was determined in enzymatic assays using recombinant human wild-type EGFR (IC50 0.5 nM) and HER2 (IC50 14 nm) (15). A panel of recombinant human kinases tested in parallel was not inhibited, demonstrating the high target specificity of afatinib. Molecular modeling revealed that afatinib binds covalently and with high affinity to Cys773 within the catalytic cleft of the ATP-binding pocket of the EGF receptor. It has been reported that this specific molecular interaction results in irreversible

inhibition of the EGFR tyrosine kinase domain (53). Experimental data from in vitro washout studies confirmed the irreversible binding of afatinib to its molecular target. In constitutively EGFR-overexpressing A431 human epidermoid cancer cells, afatinib inhibition of EGFR signaling lasted for up to 7 hours after removal of the compound from the cell cultures (15). In contrast, A431 cells exposed to reversible EGFR TKIs regained full receptor function almost immediately after inhibitor washout.

The absolute bioavailability of afatinib after oral ingestion was 45% in rats with a median tmax reached after 4 hours and a terminal half-life (t1/2) of 4.5 hours. In rats the exposure was dose proportional and no gender-related effects or compound accumulation was observed. Afatinib is primarily excreted via the feces. No relevant inhibition of cytochrome P450 isoenzymes was found. In vitro afatinib is however a CYP3A4 substrate. Since this is not considered a dominant metabolic pathway, in vivo drug-drug interactions with CYP3A4 inducers or inhibitors are not expected (15).

In human studies, afatinib showed moderately fast absorption with median tmax values between 1 h to 6 h after administration. The gMean terminal half-life (t1/2) of afatinib mainly ranged between 13 h to 57 h. In general, the maximum blood concentration (Cmax) and the integral of the concentration time curve (AUC) of afatinib increased in a dose-proportional way (15).

7.1.3 **Form**

Afatinib is supplied by Boehringer Ingelheim Pharmaceuticals, Inc as film-coated tablets in HDPE, child-resistant, tamper-evident bottles. Available dosage strengths will be 20 mg, 30 mg, and 40 mg.

7.1.4 **Storage and Stability**

Afatinib must be stored in the original packaging. Film-coated tablets are humidity sensitive and therefore bottles must be kept tightly closed. Tablets will be stored at the study site in a limited access area and must not be stored above 25 degrees Celsius.

7.1.5 **Compatibility**

N/A

7.1.6 **Handling**

N/A

7.1.7 **Availability**

Afatinib is an investigational agent and will be supplied free-of-charge from Boehringer Ingelheim Pharmaceuticals, Inc.

7.1.8 **Preparation**

N/A

7.1.9 Administration

N/A

7.1.10 Ordering

Afatinib will be ordered from Boehringer Ingelheim Pharmaceuticals, Inc. and stored in each individual study site pharmacy.

7.1.11 Accountability

The investigator or the institutional pharmacy should maintain a careful record of the inventory and disposition of the agent, as per usual clinical practice.

7.1.12 Destruction and Return

At the end of the study, unused supplies of afatinib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.2 Cisplatin

7.2.1 Description

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is a white powder with the molecular formula PtCl2H6N2, and a molecular weight of 300.05. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207°C.

Plasma concentrations of the parent compound, cisplatin, decay monoexponentially with a half-life of about 20 to 30 minutes following bolus administration of 50 or 100 mg/m2 doses. Monoexponential decay and plasma half-lives of about 0.5 hour are also seen following two hour or seven hour infusions of 100 mg/m2. After the latter, the total-body clearances and volumes of distribution at steady-state for cisplatin are about 15 to 16 L/h/m2 and 11 to 12 L/m2. Due to its unique chemical structure, the chlorine atoms of cisplatin are more subject to chemical displacement reactions by nucleophiles, such as water or sulfhydryl groups, than to enzyme-catalyzed metabolism. At physiological pH in the presence of 0.1M NaCl, the predominant molecular species are cisplatin and monohydroxymonochloro cis-diammine platinum (II) in nearly equal concentrations. The latter, combined with the possible direct displacement of the chlorine atoms by sulfhydryl groups of amino acids or proteins, accounts for the instability of cisplatin in biological matrices. The ratios of cisplatin to total free (ultrafilterable) platinum in the plasma vary considerably between patients and range from 0.5 to 1.1 after a dose of 100 mg/m2. Cisplatin does not undergo the instantaneous and reversible binding to plasma proteins that is characteristic of normal drug-protein binding. However, the platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three-hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of five days or

more. Following cisplatin doses of 20 to 120 mg/m^2, the concentrations of platinum are highest in liver, prostate, and kidney, somewhat lower in bladder, muscle, testicle, pancreas, and spleen and lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum. Platinum is present in tissues for as long as 180 days after the last administration. With the exception of intracerebral tumors, platinum concentrations in tumors are generally somewhat lower than the concentrations in the organ where the tumor is located. Different metastatic sites in the same patient may have different platinum concentrations. Hepatic metastases have the highest platinum concentrations, but these are similar to the platinum concentrations in normal liver.

Maximum red blood cell concentrations of platinum are reached within 90 to 150 minutes after a 100 mg/m^2 dose of cisplatin and decline in a biphasic manner with a terminal half-life of 36 to 47 days. Over a dose range of 40 to 140 mg cisplatin/m^2 given as a bolus injection or as infusions varying in length from 1 hour to 24 hours, from 10% to about 40% of the administered platinum is excreted in the urine in 24 hours. Over five days following administration of 40 to 100 mg/m^2 doses given as rapid, 2 to 3 hour, or 6 to 8 hour infusions, a mean of 35% to 51% of the dosed platinum is excreted in the urine. Similar mean urinary recoveries of platinum of about 14% to 30% of the dose are found following five daily administrations of 20, 30, or 40 mg/m^2/day. Only a small percentage of the administered platinum is excreted beyond 24 hours post-infusion and most of the platinum excreted in the urine in 24 hours is excreted within the first few hours. Platinum-containing species excreted in the urine are the same as those found following the incubation of cisplatin with urine from healthy subjects, except that the proportions are different. The parent compound, cisplatin, is excreted in the urine and accounts for 13% to 17% of the dose excreted within one hour after administration of 50 mg/m^2. The mean renal clearance of cisplatin exceeds creatinine clearance and is 62 and 50 mL/min/m^2 following administration of 100 mg/m^2 as 2 hour or 6 to 7 hour infusions, respectively.

The renal clearance of free (ultrafilterable) platinum also exceeds the glomerular filtration rate indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. The renal clearance of free platinum is nonlinear and variable and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion of possible tubular reabsorption. There is a potential for accumulation of ultrafilterable platinum plasma concentrations whenever cisplatin is administered on a daily basis but not when dosed on an intermittent basis. No significant relationships exist between the renal clearance of either free platinum or cisplatin and creatinine clearance. Although small amounts of platinum are present in the bile and large intestine after administration of cisplatin, the fecal excretion of platinum appears to be insignificant.

Drug Interactions – Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy. In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.

7.2.2 Form
Cisplatin Injection is a sterile aqueous solution, available in 50, 100 and 200 mL multiple dose vials, each mL containing 1 mg of cisplatin and 9 mg sodium chloride in water for injection. HCI and/or sodium hydroxide added to adjust pH to 3.5 to 4.5. It is supplied by Bedford Laboratories or other generic suppliers.

7.2.3 Storage and Stability
Cisplatin Injection is a sterile, multidose vial without preservatives.

Store at 15° to 25°C (59° to 77°F). Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

The aqueous solution should be used intravenously only and should be administered by IV infusion over a 1 hour period.

7.2.4 Compatibility
The agent should be administered separately from pemetrexed. Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for preparation or administration. Aluminum reacts with cisplatin, causing precipitate formation and a loss of potency.

7.2.5 Handling
Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.2.6 Availability
Cisplatin is a commercially available agent and should be obtained per institutional guidelines.

7.2.7 Preparation
Per institutional guidelines. See product insert for suggestions.

7.2.8 Administration
Per institutional guidelines. See product insert for suggestions.

7.2.9 Ordering
Cisplatin should be ordered according to institutional guidelines by the each individual pharmacy that is coordinating the administration.

7.2.10 Accountability
N/A

7.2.11 Destruction and Return
N/A

7.3 Pemetrexed

7.3.1 Description

Pemetrexed is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white to almost-white solid with a molecular formula of $C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$ and a molecular weight of 597.49.

Pemetrexed exerts its antineoplastic activity by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), all folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

The pharmacokinetics of pemetrexed administered as a single agent in doses ranging from 0.2 to 838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration. The total systemic clearance of pemetrexed is 91.8 mL/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 mL/min). The clearance decreases, and exposure (AUC) increases, as renal function decreases. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (Cmax) increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles. Pemetrexed has a steady-state volume of distribution of 16.1 liters. In vitro studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

Drug Interactions

Chemotherapeutic Agents — Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum are unaltered by pemetrexed.

Vitamins — Coadministration of oral folic acid or intramuscular vitamin B12 does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes — Results from in vitro studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No studies were conducted to determine the cytochrome P450 isozyme induction potential of pemetrexed, because pemetrexed used as recommended (once every 21 days) would not be expected to cause any significant enzyme induction.

Aspirin — Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Ibuprofen — Daily ibuprofen doses of 400 mg qid reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown.

7.3.2 Form

Pemetrexed is supplied by Eli Lilly as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 100 mg or 500 mg vial of pemetrexed contains pemetrexed disodium equivalent to 100 mg pemetrexed and 106 mg mannitol or 500 mg pemetrexed and 500 mg mannitol, respectively. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

7.3.3 Storage and Stability

Pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). When prepared as directed, reconstituted and infusion solutions of pemetrexed contain no antimicrobial preservatives. Discard unused portion. Pemetrexed is not light sensitive.

7.3.4 Compatibility

Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Coadministration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended.

7.3.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.3.6 Availability
Pemetrexed is a commercially available agent and should be obtained per institutional guidelines.

7.3.7 Preparation
Per institutional guidelines. See product insert for suggestions.

7.3.8 Administration
Per institutional guidelines. See product insert for suggestions.

7.3.9 Ordering
Pemetrexed should be ordered according to institutional guidelines by the each individual pharmacy that is coordinating the administration.

7.3.10 Accountability
N/A

7.3.11 Destruction and Return
N/A

8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic Studies
Not applicable.

8.2 Pharmacodynamic Studies

8.2.1 Laboratory Correlative Studies

Studies will be performed on excess pre-treatment biopsy material as well as post-treatment surgical specimen and repeat biopsy material at the time of progression when available.

8.2.1.1 Molecular Diagnostics Platform

Tumor mutation status (including *EGFR* and *KRAS*) will be determined by the multiplex molecular diagnostics platform ("SNaPshot") as described in Section 2.2.2 under the supervision of Dr. A. John Iafrate at MGH.

8.2.1.2 Determination of EGFR protein expression by immunohistochemistry (IHC)

EGFR protein expression will be determined by IHC staining of formalin-fixed tumor tissue according to standard methods at MGH. Tumor specimen will be submitted by routine pathology or via request of previously obtained specimen from outside institutions.

8.2.1.3 Determination of EGFR gene copy number by FISH analysis

EGFR gene copy number will be determined by fluorescence-in situ hybridization of formalin-fixed tumor tissue according to standard methods at MGH. The standard definition of increased *EGFR* gene copy number by FISH positivity includes tumors with: 1) four or more copies of the EGFR gene in >= 40% of the cells (high polysomy), or 2) tumors with EGFR gene amplification, defined as gene-to-chromosome ratio >= 2 and presence of gene cluster, or >= 15 copies of the gene in >= 10 % of the cells. Tumor specimen will be submitted by routine pathology or via request of previously obtained specimen from outside institutions.

8.2.1.4 Additional genomic or protein biomarkers

We also intend to investigate functional protein biomarkers as predictors of treatment outcome. Functional biomarkers have the advantage of reflecting the performance of a particular biochemical pathway upon cytotoxic stress. If patients consent to correlative study tissue collection, we will collect fresh tumor tissues from any biopsy procedure such as metastatic lymph nodes taken at the time of the staging mediastinoscopy or other procedure. Discarded viable tumor tissue in the lymph node or needle biopsy samples not required for diagnosis will be made available for this study based on availability and at the discretion of the pathologist. Tumor will be placed into nutrient medium on ice and transported by study staff expeditiously to the Laboratory of Cellular and Molecular Radiation Oncology at MGH. In order to model the treatment effect, tumor tissue will be aliquoted and depending on availability subjected to ionizing radiation, cisplatin, pemetrexed, or other agents (*ex-vivo)*. Samples will be incubated and snap-frozen for later genomic analysis and immunofluorescence microscopy. The activity of DNA repair pathways will be assessed and correlated with clinical treatment response outcome. Potential genomic or functional biomarkers associated with DNA repair or other cellular pathways will be explored. A similar analysis will be done on any residual tumor tissue found at the time of surgery.

8.2.1.5 Other Studies
Enrollment on other IRB-approved companion studies is allowed as long as these are not therapeutic and do not interfere with the current treatment protocol.

8.2.2 Circulating Tumor Cells

CTCs will be measured in freshly obtained peripheral blood using the CTC-Chip at baseline, following completion of 2 months of induction afatinib, then at the end of study visit. The association of CTC numbers with radiographic disease response and recurrence will be assessed. This assay will be performed under the supervision of Daniel Haber. Blood samples will be same-Day couriered to the laboratories of Daniel Haber in the Charlestown Navy Yard at MGH. Blood samples will be stored on a rocking platform to prevent cell settling and will be processed within 24 hours of blood draw. Whole blood will be passed through the CTC-chip using standard procedures as previously published (54, 55). Captured CTCs will be fixed on the

CTC-chip and stained to identify DNA content, epithelial cells and nonspecifically bound leukocytes. Cells staining positive for nuclear content and positive for cytokeratin will be counted as CTCs. The number of CTCs per milliliter of blood will be determined by comprehensive image analysis, scanning the entire chip and identifying CTCs based on cell size, morphology and fluorescence staining. Any excess sample material may be used by the laboratory investigators for quality control experiments or for use in developing new standard operating procedures for patients without cancer undergoing CTC chip analysis.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy unless otherwise noted. Scans must be done 28 days prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Of note, pulmonary function tests are typically obtained as part of routine pre-surgical evaluation and should be obtained within 6 months of study enrollment.

Mediastinal lymph nodes must be assessed histologically or cytologically by mediastinoscopy, EBUS, EUS, or any other appropriate procedure prior to start of therapy. N2 nodes (stage IIIA) or N3 nodes (IIIB) must be demonstrated unless the participant is determined to have stage III by other criteria (i.e., T3N1, T4N0, or T4N1).

	Pre-Study	Induction afatinib[a]		Chemoradiation						Surgical Resection	Adjuvant Chemotherapy[b]		Consol-idation	End of Treatment Visit and F/U
		C1	C2	C1, D1	C1, D8	C1, D15	C2, D1	C2, D8	C2, D15		C1, D1	C2, D1	C1-26[c]	
Afatinib		X	X										X	
Cisplatin				X			X				X	X		
Pemetrexed[d]				X			X				X	X		
Radiation Therapy				X----------X										
EGFR genotype	X									X				
CTCs	X		X											X
PFTs [e]	X													
Mediastinal LN biopsy[f]	X													
Informed consent	X													
History	X													
Physical exam (Including Height, Weight, VS) [g]	X	X	X	X	X	X	X	X	X		X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X		X	X	X	X
CBC, chemistry [h]	X	X	X	X	X	X	X	X	X		X	X	X	X
AE evaluation		X----------X												
Pregnancy test (WOCP)	X													
Determination of resectability[f]	X													
Surgery										X				
CT scan	X[i]		X[j]						X[k]		X[l]		X [m]	X[n]
PET scan	X[i]		X[j]											As clinically indicated

	Pre-Study	Induction afatinib[a]		Chemoradiation						Surgical Resection	Adjuvant Chemotherapy[b]		Consol-idation	End of Treatment Visit and F/U
		C1	C2	C1, D1	C1, D8	C1, D15	C2, D1	C2, D8	C2, D15		C1, D1	C2, D1	C1-26[c]	
Brain MRI/Head CT	X[i]								X[k]					As clinically indicated
12-lead EKG	X													
Repeat Biopsy														X[p]

a. Cycle length for induction afatinib is 4 weeks (28 days). During induction afatinib, Cycle 1 (C1) visits are on Days 1 and 8; Cycle 2 (C2) visit is on Day 1 only.

b. Adjuvant Therapy is given at the discretion of the treating physician after surgical resection (if applicable)

c. Cycle length for consolidation afatinib is 4 weeks (28 days). Only patients with tumor shrinkage including 0%, partial response, or complete response by RECIST during induction afatinib will receive consolidation afatinib. Unless otherwise noted, patients who receive consolidation afatinib are evaluated monthly on Day 1 of cycles 1-4 and then every 3 months on Day 1 of cycles 5-26 (cycles 7, 10, 13, 16, 19, 22, 25). Patients who do not receive consolidation afatinib are evaluated every 3 months.

d. Patients should start daily folic acid supplementation and receive a B12 injection at least 5 days prior to beginning pemetrexed. B12 should be re-administered approximately every 9 weeks while patient is receiving pemetrexed. Folic acid and B12 should continue until 3 weeks after the final dose of pemetrexed.

e: PFTs must include FEV1 and DLCO, within 6 months of study entry

f: Mediastinal lymph node (LN) biopsy must be performed before start of treatment but does not need to be within a 28-day window and may be performed either before or after informed consent is obtained. Documentation of surgical resectability status by a surgeon does not need to be within a 28-day window of starting induction therapy

g: Vital signs include BP, RR, HR, oxygen saturation, and temperature

h: CBC with differential, basic metabolic panel (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium), magnesium, liver function tests (albumin, total protein, alkaline phosphatase, total anddirect bilirubin, ALT, AST). Direct bilirubin is only required at screening

.**i**. CT of the chest/abdomen/pelvis, PET scan, and Brain MRI or CT must be performed during screening

j. After induction afatinib is completed, CT of the chest for restaging and radiation planning (neck CT may be needed depending upon disease extent) and A PET scan to further evaluate response to treatment should be performed. For participant convenience, these tests may be combined into one study (i.e. PET/CT of the chest and potentially the neck). If an individual patient is unable to undergo the PET scan, exceptions may be granted after discussion with the PI.

k. Most surgeons will request restaging CT scans and/or brain MRI prior to surgery but this is at the discretion of the treating physicians and is not required

.l. Chest CT is required between 6 and 10 weeks after surgical resection for all patients undergoing surgery, and should be done prior to start of adjuvant therapy if applicable. If no surgery was performed, Chest CT is required between 6 and 10 weeks after completion of definitive radiation therapy

m. CT scan of the chest will occur during consolidation afatinib q3 mo for 1 year, then q6 mo for 1 year. This means scans will occur prior to Cycle 1, 4, 7, 10, 13, 19, and 25. If a patient did not receive adjuvant chemotherapy, the CT scan obtained 6-10 weeks after surgery or definitive chemoradiation can be considered their prior to cycle 1 of consolidation afatinib scan and this does not need to be repeated. If a patient did receive adjuvant chemotherapy, a new

baseline CT scan should be obtained prior to consolidation afatinib If a patient discontinues consolidation afatinib before their prescribed 2 years is complete, they should still follow the same surveillance CT schedule as if they were still on drug.. For those not on consolidation afatinib, see footnote n.

n: Chest CT scans should be continued after consolidation afatinib (or after the period of prescribed consolidation afatinib if discontinued early) as follows – every 6 months during the 3rd year and once per year during the 4th year. For those who were not eligible to receive consolidation afatinib, the schedule of CT scans after completion of chemotherapy, radiation and potentially surgery is every 3 months during the first year, every 6 months during years 2 and 3, and once during year 4. After the completion of the 4th year, follow-up is at the discretion of the treating doctor.

o. Repeat biopsy is suggested at the time of progression

10. MEASUREMENT OF EFFECT

Participants will be assessed by RECIST criteria version 1.1 after induction afatinib as well as after concurrent chemotherapy/radiation prior to surgical resection. For patients who go for surgical resection after the restaging scan, no confirmatory scan will be possible. For those who are not able to have surgery, follow-up scans will be used for confirmation of response.

10.1 Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (56). Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of Cycle 1 will also be considered evaluable.)

10.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter > 10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with $\geq$ 10 to < 15 mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

Target lesions. The primary lung tumor and the hilar/mediastinal lymph nodes judged as involved should be identified as the ***target lesions*** and recorded and measured at baseline and with each follow-up imaging evaluation.

The longest diameter (LD) of *the target lesions* will be calculated from the pre-treatment diagnostic chest CT scan with iv contrast, using pulmonary windowing for the primary tumor soft tissue windowing for involved lymph nodes, and reported as the baseline LD. The baseline LD will be used as a reference by which to characterize the objective tumor response.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that over time may coalesce with the residual tumor. In cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, a PET/CT scan should be obtained for further characterization. If findings remain indeterminate, it should be assumed that the observed abnormalities represent residual tumor.

Non-target lesions. All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Conventional CT. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (57). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

10.1.4 Response Criteria

Complete Response (CR): Disappearance of all target lesions; this will be made based on CT image evaluation.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD; ideally, this will be made based on CT image evaluation.

Progressive Disease (PD): At least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (new lesions must be > slice thickness). Ideally, this determination will be made based on CT image evaluation**.** If the criteria for PD are met, the patient should undergo either PET scan imaging and/or a direct biopsy of the targeted tumor for evaluation as to whether local failure (LF), regional failure (RF), and/or distant failure (DF) exists as defined below. For diagnosis of brain metastases, a brain MRI with gadolinium is sufficient.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Local failure (LF) – Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria: 1) Increase in tumor dimension of 20% as defined above for progressive disease. 2) The measurable tumor with criteria meeting PD should be avid on PET imaging with uptake of a similar intensity as the pretreatment staging PET, or the measurable tumor should be biopsied confirming viable carcinoma. Marginal failure, i.e., PET-positive or biopsied measurable tumor within 1 cm of the PTV, will be counted as LF. The EORTC criteria for post-treatment PET evaluation may be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathologic for cancer recurrence vs. inflammation (58). Hence, patients undergoing total removal of the primary lung tumor via a lobectomy or pneumonectomy following preoperative therapy, will in most cases not be at risk for LF unless there is a positive or close surgical resection margin. LF will be scored with or without preceding DF.

Regional failure (RF) – This is defined as progression of nodal target lesions or the appearance of non-target lesions in either hilum, the mediastinum, or supraclavicular fossa. The measurable tumor with criteria meeting PD should be avid on PET imaging with uptake of a similar intensity as the pretreatment staging PET, or the measurable tumor should be biopsied confirming viable carcinoma.

Distant failure (DF) – This is defined as the radiographic appearance suspicious for carcinoma and having a dimension of at least 1 cm. Intra-thoracic failure at least 1 cm away from the radiation PTV will also be scored as DF unless pathological or genetic analysis of the new lesion suggests that it is a metachronous lung cancer. A final determination may be made by the study PI or his designee. Distant disease should be confirmed by FDG avidity on PET scan and/or biopsy. Intracranial metastasis should be confirmed by MRI with gadolinium.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

10.1.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from date of enrollment to time of objective disease progression, either local, regional, or distant. Progression will be divided into two categories: locoregional failure and distant failure. Locoregional failure is progression or recurrence of disease present on the baseline CT scans. Distant failure is the development of new lesions at a metastatic site. Death will also be regarded as a progression event.

10.1.6 Response Review

All staging films will be reviewed centrally at DF/HCC by the Tumor Imaging Metrics Core.

10.2 Conversion to operable cases

Conversion to operable case is defined as a participant who was determined to be inoperable by a thoracic surgeon at baseline but then proceeds to surgical resection following chemoradiation.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

An AE of Special Interest includes hepatic injury defined by the following alterations of liver parameters (measured in the same blood draw sample): for patients with normal AST/ALT and bilirubin at baseline, an elevation of AST and/or ALT above > 3 fold ULN combined with an elevation of bilirubin above > 2 fold ULN. Patients showing these lab abnormalities need to be followed up appropriately.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is defined as any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is immediately life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24 hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is deemed serious for any other reason if it is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- Administrative or social reasons during the trial (e.g. days on which infusion takes place, long distance from home to site, etc.)
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

These and other hospitalizations planned at the beginning of the trial do not need to be reported as an SAE.

11.1.3 Severity of adverse event

The severity of the AE should be judged based on the following:

The severity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

11.1.4 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.4.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk. Note that previously identified adverse events for afatinib can be found in the "listed adverse events" section of the most recent version of the afatinib Investigator's Brochure.

11.1.4.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.5 Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship must be recorded for each adverse event. Causality will be reported as either "Yes" or "No".

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

11.1.6. Malignant disease progression

Expected fluctuations or expected deterioration of the underlying disease should not be recorded as an AE unless at least one of the following criteria is met:

- the worsening of the disease constitutes an SAE,
- additional treatment is required, i.e. concomitant medication is added or changed.
- An unexpected deterioration from baseline has occurred in the opinion of the investigator.

11.1.7 Worsening of pre-existing conditions

A pre-existing condition present at baseline, which remains unchanged during the trial, does not need to be recorded as adverse event. Any worsening of any pre-existing baseline condition should be reported as an adverse event. Examples of worsening of a preexisting condition that should be recorded as an AE are given below:

- Worsening of condition meets the criteria for an SAE
- Action is taken with the investigational drug (i.e. dose is reduced or treatment is discontinued)
- Treatment is required (concomitant medication is added or changed)
- The investigator believes a patient has shown a clear deterioration from baseline symptoms

11.1.8 Special considerations for post-operative AE's

- Major morbidities are scored as any event occurring within 30 days following surgery.
- Reports should document duration of surgery; estimated blood loss; blood transfusions required intra- and perioperatively; and number of postoperative days intubated.

- The Adverse Events attributed to surgery will include but are not limited to any of the following complications listed below:
  - Infection (includes any infection of incision site[s]; this includes wound infection of surgical incisions for thoracotomy). When there is a wound infection, specify the organism causing the infection in the space provided, and record which surgical incision[s] was infected.
  - Fistula, pulmonary/upper respiratory (includes any fistula that developed within the postoperative period; A patient with a bronchopleural fistula associated with an intrathoracic infection should be reported as having both the intrathoracic infection and a fistula, pulmonary/upper respiratory.)
  - Atelectasis (includes collapse of either an entire lung or a lobe of the lung or atelectasis severe enough to require medical/operative intervention;
  - Pneumothorax (includes lung collapse that is due to air leakage from the lung into the pleural space; to be reported here, the pneumothorax must be severe enough that treatment, i.e., insertion of reinsertion of a chest tube is required.)
  - Chest tube drainage or air leak (includes bronchial stump leak)
  - Pleural effusion (non-malignant) [includes any effusion within the postoperative period that requires treatment, i.e., pleural tap.]
  - Chylothorax
  - Cardiac ischemia/infarction (includes any myocardial infarction that occurred within the postoperative period.)
  - Thrombosis/thrombus/embolism (includes any pulmonary embolus that occurred within the postoperative period.)
  - Supraventricular and nodal arrhythmia (includes any new atrial arrhythmia that developed within the postoperative period that requires treatment.)
  - Ventricular arrhythmia (includes any new ventricular arrhythmia that developed within the postoperative period that requires treatment.)
  - Hemorrhage/bleeding associated with surgery, intra-operative or postoperative
  - (Postoperative period is defined as ≤ 72 hours after surgery; includes hemorrhage that required reoperation for control.)
  - All deaths with the attribution of definite, possible, or probable resulting from protocol surgery must be communicated to the study PI or his designee within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.
    - All deaths during and within 30 days of completion of protocol surgery, regardless of attribution, must be reported by telephone within 24 hours of discovery to the study PI or his designee.
- All life-threatening (an event which in view of the investigator, places the patient at immediate risk of death from the reaction) and Grade 4 events that are related, possibly related, or probably related to protocol treatment must be reported to the study PI within 24 hours of discovery.
- All applicable data and a written report from the PI must be submitted within 10 working days of the report of any fatal adverse event with the attribution of definite, possible, or probable relation to protocol treatment and for grade 4 or life-threatening events.

11.2 Procedures for AE and SAE Recording and Reporting

Upon inclusion into a trial, the patient's condition is assessed (e.g. documentation of history / concomitant diagnoses and diseases), and relevant changes from baseline are noted subsequently.

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the trial defined follow-up period) will be collected, documented and reported by the investigator. For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the expectedness of the investigational drug to the AEs as defined in the Listed Adverse Events section of the Boehringer Ingelheim's (BI's) current Investigator Brochure for the Product.

The investigator must report events to the pharmaceutical company via telephone/fax using the SAE report as per the timelines specified in the Pharmacovigilance agreement.

The descriptions and grading scales found in the CTEP v4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP CTCAE v4.0 is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP v4.0 of CTCAE.

11.3 Reporting to the Study Sponsor

11.3.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

In addition to reporting SAEs, the following should be reported:
- Non-serious AEs occurring at the same time and/or which are medically related to the SAE
- AEs of Special Interests independent from their seriousness.

Report serious adverse events by telephone or facsimile to:

Beth Kennedy
101 Merrimac Street, Room 2-220
Boston, MA 02114-4719
Phone 617-724-1223
Fax 617-724-0599

Principal Investigator 24-Hour Contact:
Lecia Sequist, MD, MPH (Overall Study PI)
617-724-4000

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.3.2 Non-Serious Adverse Event Reporting
Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.4 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

11.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.6 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or 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).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last Day of the cycle
Adverse Event Report Form	Within 10 days of the last Day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet as required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all Grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data 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.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines
N/A

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints
This study will enroll patients with stage III NSCLC who have not undergone prior treatment for their disease. Subjects will receive 8 weeks of afatinib, followed by radiological evaluation to determine the responsiveness of their disease to the drug. This will be followed by concurrent chemotherapy with cisplatin and pemetrexed and conformal individualized radiation therapy. Definitive local treatment will be completed with either surgery or radiation if the patient is considered inoperable. Participants may also receive adjuvant chemotherapy at the discretion of the clinician. Those patients who had a response to induction afatinib according to RECIST criteria will receive personalized consolidation treatment with afatinib for up to 2 years following the completion of local therapy.

The primary endpoint of this trial is to investigate the response rate to induction afatinib. Response will be scored using RECIST criteria and will include both partial responses and complete responses after 2 months of induction afatinib. Note that none of the patients will have a confirmatory scan performed (4 weeks after initial response noted), because all patients will go on immediately to the next phase of treatment – concurrent chemoradiation.

A maximum of 30 patients will be enrolled in this study. The response rate to afatinib among EGFR mutants in the metastatic setting is up to 62% (11), so we expect a response rate of at least a response rate of 65% in patients with locally advanced disease. A sample size of 30 patients will provide 87% power to detect the expected induction response rate of 65% (meaning that at least 17 patients responded). If 16 or fewer patients respond, this strategy will be deemed not interesting for further study as a response rate of < 50% makes delaying standard chemotherapy and radiation in favor of induction EGFR TKI therapy clinically unappealing. The decision rule is associated with only 14% probability of declaring success should the underlying response rate actually be 45% or less.

14.2 Sample Size/Accrual Rate
At the MGH, ~30% of all NSCLC patients present with stage III disease. Over the course of 1 year, genotyping was performed on ~500 patients, approximately 15% of whom were found to have an EGFR mutation. Thus, ~20 eligible patients are seen at MGH per year, and assuming a conservative 50% accrual rate from all possibly eligible patients, we expect to be able to accrue 10 patients per year. In addition, participation by the Dana-Farber Cancer Institute and North Shore Medical Center would roughly double the number of eligible patients. Thus, we would expect to complete enrollment of 30 patients in about 2 years and have sufficient follow-up to report results on the PFS primary endpoint in ~4-5 years.

14.3 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed for exploratory purposes only.

14.3.1 Progression-free and overall survival rates

Progression free survival (PFS) rates at 2 years as well median PFS times will be calculated from the endpoints described in Section 10, namely absence of local, regional, and distant failures, as well as death. For the calculation of 2 year overall survival (OS) rates and median OS time, death events will be recorded. All time-to-event variables will be recorded from the Day of study enrollment.

14.3.2 Safety

Toxicity will be assessed using CTC v4.0 criteria. All participants who receive any amount of study drug will be evaluable for toxicity.

14.3.3 Conversion to operable cases

The rate of conversion to operable cases will be calculated based the clinical determination of operability status by the thoracic surgeon at baseline and during week 5 of radiation therapy.

14.3.4 Local and regional tumor control and rate of distant failure

Crude frequencies and rates of isolated local and regional recurrence, as defined in Section 10, as well as crude frequencies and rates of distant metastases (defined as the development of metastatic disease outside of the thorax, with or without concurrent local/regional failure) will be calculated. Isolated local and regional failures are defined as the absence of distant failure within one month of the diagnosis of local or regional recurrence.

14.3.5 Association of biomarkers and treatment outcomes

Exploratory, hypothesis-generating analyses will be performed to correlate any findings from the various potential biomarker studies listed in Section 8 with the primary and secondary study endpoints as above.

14.4 Reporting and Exclusions

14.4.1 **Evaluation of toxicity.** All participants will be evaluable for toxicity from the time of their first treatment.

14.4.2 **Evaluation of response.** Patients who received no study treatments will not be evaluated for response to treatment. All other participants included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.

Each participant should be assigned one of the following categories (based on the definitions of treatment outcome defined in Section 10):

1) Alive without evidence of tumor recurrence locally, regionally, or distantly,
2) Isolated local failure,
3) solated regional failure,
4) Distant failure with or without concurrent local or regional failure,
5) Early death from malignancy,
6) Early death from toxicity,
7) Early death from other cause,
8) Unknown (not assessable, insufficient data).

For each participant, the best clinical response of the locoregional tumor to non-surgical therapy may be categorized as:
a) complete response,
b) partial response, or
c) stable disease.

All of the participants who met the eligibility criteria and were enrolled, except patients who did not receive any study medication, will be included in the main analysis of the response rate and calculation of survival. Participants in response categories 2-5 will be considered to have a treatment failure (disease progression).

15. PUBLICATION PLAN

It is anticipated that the first report from this study will provide the response rate to induction therapy with afatinib as well as the conversion rate from non-operable to operable cases. A more mature follow-up report will provide the 2 year progression-free survival statistics. Both reports will likely be presented first in abstract form, then in peer-reviewed manuscripts.

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17. APPENDICES

Appendix A – AJCC 7th edition lung cancer staging

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	N3	M0
Stage IV	Any T	Any N	M1a,b

Appendix B: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix C: Cockcroft-Gault Formula for Creatinine Clearance

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