EValuation of Erlotinib as a Neoadjuvant Therapy in stage III NSCLC patients with EGFR mutations (EVENT trial)

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Study Agents and Their Suppliers:

1. Erlotinib Hydrochloride (OSI-774; Tarceva®), IND# 53728, Astellas /Genentech BioOncology.FDA approval date: 18-Nov-04. Erlotinib, clinical trial material that is "commercial in nature" will be provided by the sponsor. **Study is IND exempt approved by the FDA**

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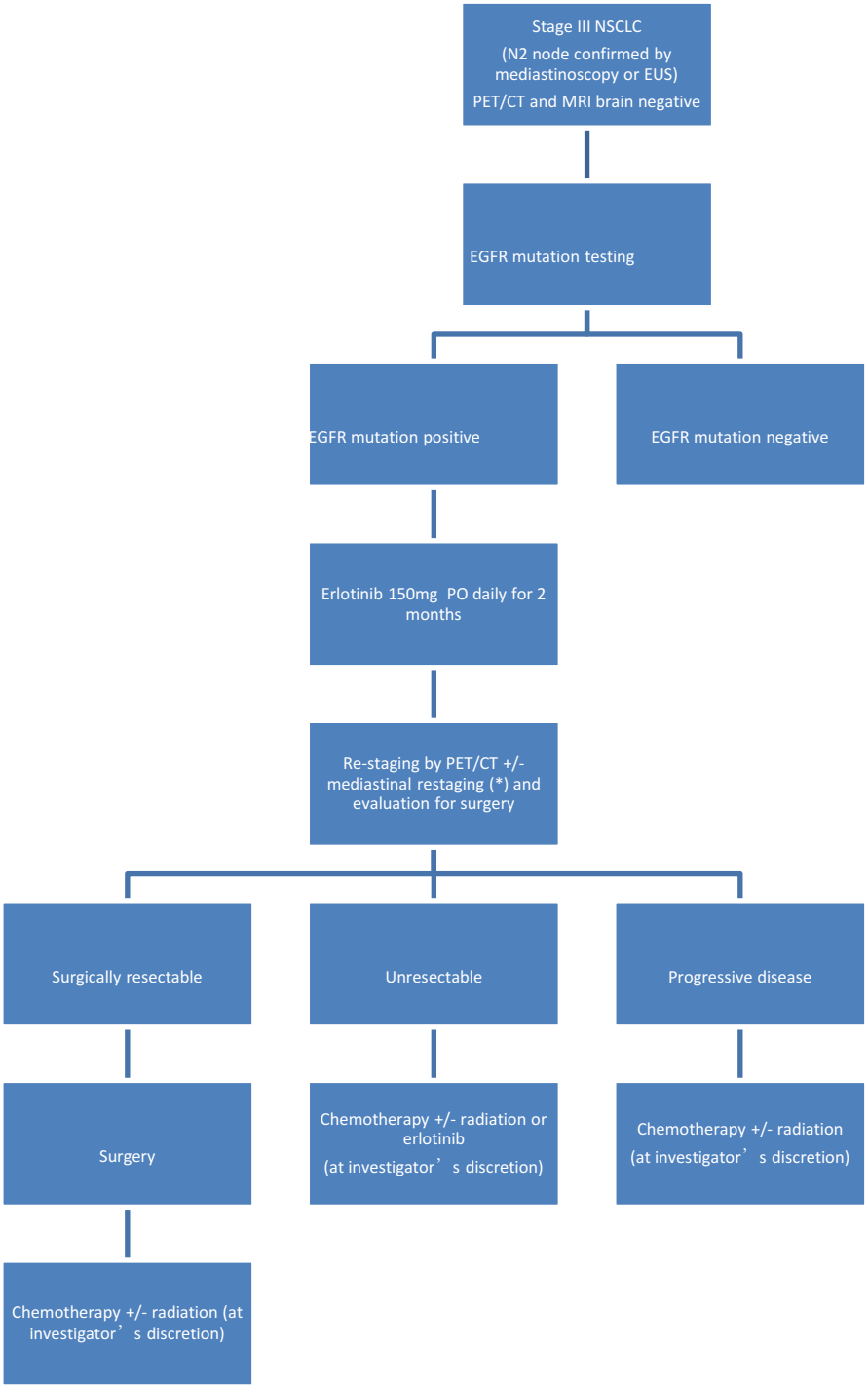
SCHEMA



* Patients with non-progressive disease who are not going for surgery should have mediastinal restaging done by either EUS/EBUS or mediastinoscopy

1.0 OBJECTIVES:

1.1 Primary Objective

- To estimate the rate of mediastinal nodal clearance and complete pathological response after neoadjuvant erlotinib in patients with EGFR mutated stage III NSCLC.

1.2 Secondary Objectives

- To determine the progression free survival in patient population of EGFR mutated stage III NSCLC patients who are treated with neoadjuvant erlotinib therapy
- To determine the overall survival (exploratory objective)
- To estimate the overall response rate from neoadjuvant erlotinib
- To estimate the surgical resection rate
- To evaluate the safety of neoadjuvant erlotinib

1.3 Objectives of correlative studies

- The objectives of the correlative studies are: to determine several molecular and cellular biomarkers in the **tumors**, the **skin** and the **serum** that are predictive of the efficacy of neoadjuvant erlotinib. Formalin-fixed, paraffin-embedded tumor (FFPE) blocks or slides from the original diagnosis and at the time of surgery, fresh frozen tumor samples, skin samples (optional), and peripheral blood will be collected from study patients who consent to these studies at the time of pre- and post-treatment. (We acknowledge here that a significant portion of the patients will not have both pre and post-specimen due to expected high response rate to erlotinib therapy)

2.0 BACKGROUND:

Stage III NSCLC:

Lung cancer is the most common cause of cancer mortality in the United States and throughout the world. Approximately 213,000 new cases are estimated to be diagnosed in 2007.[1] At initial presentation, fewer than one-half of patients will have surgically resectable lung cancer. Approximately one-quarter of patients will present with locally advanced stage III disease. Historically, stage III lung cancer was defined as locoregionally advanced disease due to primary tumor extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3) without evidence of distant metastases (M0).[2] With the 2009 revisions to the TNM staging

system, stage III lung cancers now include T3 tumors greater than 7 cm in size and T3 tumors with multiple nodules in the same lobe, when associated with N1 involvement.[3]

Most patients are not considered candidates for immediate surgical resection and typically treated with combined modality therapy utilizing chemotherapy concurrently with radiation.[4] Depending on the extent of loco-regional disease; some patients are locally unresectable and receive definitive chemoradiation while other patients receive a lower dose of neoadjuvant chemoradiation followed by attempted surgical resection.

Outcome from clinical trials in Stage III NSCLC:

Depending on clinical circumstances, the principal forms of treatment that are considered for patients with locally advanced stage III NSCLC includes surgery, radiation therapy (RT), chemotherapy, or combinations of these modalities. The management of stage III NSCLC usually requires a multidisciplinary combined modality approach.

Prior to the recognition of the benefits of systemic chemotherapy for patients with metastatic NSCLC, the standard of care for patients with locally advanced unresectable or inoperable disease was radiotherapy. A meta-analysis based on individual data from 3033 patients from 22 trials demonstrated a statistically significant benefit of combining chemotherapy with radiation for these patients (Non-Small Cell Lung Cancer Collaborative Group 1995). The greatest difference was seen in the 12 cisplatin-based trials involving 1780 patients. The hazard ratio (HR) in favor of cisplatin 0.87 (p=0.005) corresponded to an absolute reduction in the risk of death of 4% at 2 years, and 2% at 5 years.[5]

A recent individual patient-based meta-analysis examined the role of chemotherapy given either sequentially or concomitantly with radiation compared to radiation alone.[6] A separate meta-analysis examined and compared the results of randomized trials of concomitant chemotherapy and radiation therapy (ChRT) with sequential chemotherapy and radiation.[7] There were 4917 patients in the 31 trials examining sequential chemotherapy and radiation to radiation alone. Data were available from 22 trials comprising a total of 3839 patients. Sixteen trials used platinum-based regimens and 15 of the trials used a radiation dose below 60 Gy. **Combined modality therapy improved survival (HR=0.88; p<0.001), corresponding to an absolute benefit in survival of 2.7% at 3 years.** There was no detectable interaction between the timing of the administration of chemotherapy or the nature of the drugs used with survival.[6]

There were 3332 patients in 21 trials that examined concomitant ChRT to radiation alone with data available for analysis from 2910 patients in 16 trials. Chemotherapy was administered daily or weekly in the majority of trials and only 308 patients did not receive a platinum agent. Concomitant therapy produced a survival advantage (HR=0.87; p<0.001), corresponding to an absolute increase in survival of 3.2% at 3 years and 1.2% at 5 years. There was no evidence of benefit to subgroups based on timing of chemotherapy (daily, weekly, or other) or the addition of induction chemotherapy. The most favorable hazard ratios were seen with platinum and etoposide combinations or with

taxanes alone, but the numbers of patients were small and the results were not conclusive.[6]

A separate analysis focused on examining trials comparing sequential chemotherapy and radiation with concomitant ChRT.[7] Data from 6 trials encompassing a total of 1205 patients were assessed; 97% of patients had Stage IIIA or IIIB disease, with 97% having performance status of 0 or 1. While there was no difference seen in pulmonary toxicity between the sequential and concomitant groups, the relative risk of Grade 3 or 4 esophagitis was higher in the group treated with concomitant therapy (relative risk [RR]=4.9; $p<0.0001$). There was improved survival in the concomitant group (HR=0.84; $p=0.004$), translating to an absolute improvement in survival of 5.7% at 3 years. Compared to the sequential group survival of 10.6% at 5 years, the survival of 15.1% at 5 years in the concomitant group represented an absolute increase of 4.5%. These benefits seem primarily attributable to a decrease in locoregional progression in the concomitant group, albeit at the expense of increased esophageal toxicity.[7]

Current standards of chemotherapy given to patients with metastatic disease cannot be given at full doses safely with radical doses of thoracic radiation.[8] It is possible to hypothesize that the lack of improvement in systemic control seen in the meta-analysis reported by Auperin and colleagues (2007) may be either a reflection of the undertreatment of occult systemic disease by outdated regimens given at full dose or the use of standard chemotherapy regimens at suboptimal doses.[4]

The conclusion arising from these efforts is that concurrent ChRT produces the highest cure rates. However, **the median survival in most of these trials remains 20-24 months and the progression free survival of 12-13 months.**

Chemotherapy Prior to or Post Chemo/RT Has Not Improved Survival as Compared to Chemo/RT Alone:

Chemoradiation is a loco-regional modality. After chemoradiation the majority of patients develop systemic metastases which ultimately cause death. Additional chemotherapy either before or after chemoradiation has not improved survival. The recent Hoosier Oncology Group phase III trial demonstrated no improvement in outcome with the addition of three cycles of docetaxel 75mg/m^2 after definitive chemoradiotherapy as compared to chemoradiation alone.[9] The control group had a progression free survival of 12.9 months compared to 12 months for the docetaxel arm. Median overall survival was 24.1 months for the observation arm and 21.5 months for the docetaxel arm.

CALGB 39801 demonstrated no improvement with induction chemotherapy prior to chemoradiation as compared to chemoradiation alone.[10] Two year overall survivals were 29 % and 31%.

In unselected group of patients, the addition of the EGFR small molecule tyrosine kinase inhibitor gefitinib after chemoradiotherapy and consolidation chemotherapy failed to improve progression free survival or overall survival in a phase III SWOG trial.[11]

Role of surgery in patients with Stage III NSCLC

The role of surgery in patients with clinically stage IIIA NSCLC remains uncertain.[4] Two large randomized studies examined the role of surgery in potentially resectable stage III NSCLC. A phase III Intergroup 0139 trial compared definitive chemoradiotherapy versus concurrent chemotherapy and 45Gy of radiation followed by surgery.[12] the most recently updated data has shown a statistically significant improvement in 5 year progression free survival for the surgical arm of 22% vs 11% without a statistically significant overall survival benefit due to early surgical mortality.

In the EORTC trial, patients with potentially resectable stage III disease were treated with three cycles of chemotherapy and then randomized to either surgery or radiation. The primary endpoint was overall survival. The reported 5year overall survival in the radiation arm and surgery arm were 14% and 15.7% respectively. However, the surgical resectability rate in the surgical arm was only 50%.[13]

Based on these trials, it is a general consensus that the surgical resection after a standard chemoradiation adds little value over continuation of chemoradiation. However, both of the trials had significant flaws and in practice the surgical evaluation is done for patients with stage III disease who are appropriate candidate for surgery after initial induction therapy. **There is an unmet need to develop more effective, targeted therapies as an initial induction or neoadjuvant therapy for patients with stage III NSCLC.**

Prognostic value of mediastinal node clearing after neoadjuvant:

In the trials evaluating the role of surgery in stage III NSCLC patients, patients who had nodal clearance (N0 in final pathology) or mediastinal down staging (N0, N1 disease in final pathology) after preoperative or neoadjuvant therapy has the best long term survival. In the Intergroup 0139 trial, nodal clearance (pN0) in the surgical group was 37%. In the surgical group, the best outcome was seen in patients who have N0 disease after neoadjuvant therapy. The 5yr survival rates are any TN0: 41%; any TN1-3: 24% and no surgery: 8%.[12]

In the EORTC trial, the rate of mediastinal down-staging in the surgery group was 25% ypN0 and 16% ypN1. The best outcome was seen in patients who had mediastinal down-staging (ypN0, N1 group) with the 5year survival rate of 29%.[13]

There are also several large prospective and retrospective studies confirming that sterilization of mediastinum as an important predictor of good outcome after neoadjuvant therapy and surgical resection. In a large prospectively collected database of 136 patients with stage IIIA disease who had surgical resection after neoadjuvant therapy, the 5 year

overall survival rate was 33%. Patients with pathological down staging (N0, N1) had improved 5year survival of 45% vs. 20% in the group without mediastinal downstaging.[14]

In another series of 92 patients with pathologically proven N2 disease who underwent surgical resection after induction chemotherapy, the 5 year overall survival was 33% and again the patients who had mediastinal down staging had better 5 year overall survival of 49 vs. 27%.[15]

Based on the results of the above mentioned studies, **the mediastinal nodal clearance after neoadjuvant therapy is a very good surrogate marker for long term survival**. The mediastinal nodal clearance can serve as a surrogate primary endpoint for long term survival in evaluating newer preoperative or neo-adjuvant therapy for patients with stage III NSCLC.

EGFR Signaling Transduction Pathway and Erlotinib HCL (Tarceva®) in NSCLC

Epidermal growth factor receptor (EGFR, also known as HER1 or erb B) is a member of the ErbB tyrosine kinase receptor family, which also includes HER2, HER3, and HER4.[16] The ErbB receptors are present in the plasma membrane and share a common structure composed of an extracellular ligand-binding domain, transmembrane segment, and an intracellular tyrosine kinase domain. ErbB receptors are activated by a variety of receptor-specific ligands including epidermal growth factor (EGF), transforming growth factor-alfa (TGF-α), amphiregulin, heparin-binding EGF (HB-EGF), epiregulin, neuregulin, and betacellulin. As a result of ligand binding, receptor dimerization, trans-autophosphorylation, and initiation of signaling occur. Several major signaling pathways mediate the downstream effects of EGFR activation: the cell proliferation pathway (Ras/Raf/MAP kinase), and survival pathway [phosphatidylinositol 3-kinase (PI3K)/Akt and Jak/Stat or protein kinase C (PKC)]. Many carcinogenic processes are mediated by EGFR signaling including cell survival, proliferation, angiogenesis, and invasiveness.[16-21]

Erlotinib (Tarceva® formerly OSI-774), a quinazoline derivative, is a potent and highly selective, small tyrosine kinase inhibitor that blocks the intracellular tyrosine kinase autophosphorylation, and subsequently prevents the receptor-mediated signaling pathways.[17] It reversibly competes with the adenosine triphosphate (ATP) at the ATP-binding site within the intracellular tyrosine kinase (TK) domain of the EGFR protein. Its mechanisms of action and clinical development have been extensively reviewed.[17-21] Erlotinib inhibits the growth of tumor cells, interferes with cell cycle progression, causing accumulation in G1 phase, and induction of apoptosis of a variety of tumor cell lines *in vitro* and *in vivo*.[22] In phase I studies, the recommended phase II dose and schedule was 150 mg daily by mouth. The minimum plasma steady-state concentrations was above the targeted concentration at 1.20 ± 0.62 μg/mL, and the mean half-life was about 24 hours. The most common side effects and dose-limiting toxicities were skin rash and diarrhea.[39] Perez-Soler et al reported that erlotinib has a single agent activity of 12.3% in 57 EGFR+ patients with advanced NSCLC who failed first-line cisplatin-containing chemotherapy. Treatment was well tolerated, the most common adverse effect being a maculopapular acneiform rash in 44 pts (78%). In 731 EGFR unselected patients, a double-blind, international, randomized trial (BR.21) comparing erlotinib 150 mg by mouth daily to

placebo, erlotinib had a response rate of 8.9%, as compared to the placebo had a response rate of less than 1 percent (p <0.001). The median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (hazard ratio, 0.61, adjusted for stratification categories; P<0.001). Overall survival was 6.7 months and 4.7 months, respectively (hazard ratio, 0.70; P<0.001), in favor of erlotinib. Five percent of patients discontinued erlotinib because of toxic effects.[24,39] On November 18, 2004, the FDA approved erlotinib for treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Erlotinib in EGFR mutated NSCLC:

One of the major advances in the treatment of NSCLC over last several years has been identification of subgroup of patients who will benefit from targeted therapies. The mutations in EGFR tyrosine kinase domain was first described in 2004.[26,27] Multiple prospective studies have proven that mutations in the *EGFR* tyrosine kinase domain are the best predictors of response and progression-free survival benefit with *EGFR* TKI. Over 80% of the mutations in *EGFR* are in frame deletions in exon 19 (del E766-A750) or point mutations in exon 21 (L858R). These mutations destabilize the kinase auto-inhibitory loop leading to constitutive activation of the receptor. The initial data defining the EGFR mutation as a predictor were derived from phase II studies in which all patients received treatment with erlotinib or gefitinib, and these have subsequently been confirmed in larger, phase III trials.[28-30]

Although mutations are clearly more common in adenocarcinomas, from women and never smokers, recent studies have identified EGFR mutations in smoker as well as males. **In a multi-institutional study conducted in Spain, *EGFR* mutations were found 350 (17%) of 2,105 patients.** The incidence of *EGFR* mutations was 8%, 10%, and 6% in men, former, and current smokers, respectively.[31] In a large study reported by the group from Memorial Sloan Kettering Cancer Center, ***EGFR* mutations occur with an incidence of 23% in 2,142 patients with stage I through IV lung adenocarcinoma.** Tumors from 19% of men and 13% of current/former smokers harbor *EGFR* sensitizing mutations. Although there is a decrease in the incidence of mutations with increased number of pack-years smoked, a substantial number of *EGFR* mutations were found in patients with a significant history of smoking. *EGFR* mutations in men and former/current smokers represent 31% and 40%of all mutations, respectively**. In addition, the incidence of EGFR mutation is very similar between early stage (stage I-IIIA) and advanced stage patients. Among 1,085 patients with stage I to IIIA, 218 patients (20%) had EGFR mutations.[32]**

In patients with advanced stage IV disease, initial treatment with an EGFR TK inhibitor has been compared with cytotoxic chemotherapy in multiple phase III trials. The most extensive data come from the IPASS trial, in which 1217 patients were randomly assigned to either gefitinib or chemotherapy with carboplatin plus paclitaxel. Patients were included based upon clinical criteria consistent with responsiveness to gefitinib; all had adenocarcinoma and were either never smokers or former light smokers (≤10 pack-years and none for at least 15 years). For the entire cohort, progression-free survival was significantly better with gefitinib compared to chemotherapy (12-month progression-free rate 25 versus 7 percent, HR 0.74). However, the difference in overall survival was not

statistically significant (median 18.8 versus 17.4 months, HR 0.90, 95% CI 0.79-1.02).[33]

Results were dependent upon the EGFR mutation status. EGFR mutations were present in 60 percent of the 437 evaluable patients, and among these, 96 percent had either an exon 19 deletion or the exon 21 L858R mutation. For patients whose tumors contained an EGFR mutation, progression-free survival was significantly prolonged with gefitinib in contrast to carboplatin plus paclitaxel (median 9.5 versus 6.3 months, HR 0.48).[33] However, overall survival was not increased with gefitinib (median 22 months in both groups, HR 1.00). Among mutation positive patients who initially received carboplatin plus paclitaxel, 64 percent subsequently were treated with an EGFR tyrosine kinase inhibitor. For those without an EGFR mutation, progression-free survival was significantly shorter with gefitinib (median 1.5 versus 6.5 months, HR 2.85, 95% CI 2.05-3.95).[33] However, the difference in overall survival was not statistically significant (median 11.2 versus 12.7 months, HR 1.18). Among those initially assigned to gefitinib, 76 percent subsequently received chemotherapy, most of which was platinum-based.

In the OPTIMAL trial from China, 154 patients with known EGFR mutations and measurable disease were randomly assigned to erlotinib or gemcitabine plus carboplatin.[34] **Treatment with erlotinib significantly improved progression-free survival (13.1 versus 4.6 months, HR 0.16, 95% CI 0.10-0.26). Similarly, the objective response rate was significantly improved with erlotinib (83 versus 36 percent).** [34]

In the EURTAC trial, 174 patients with EGFR mutations were randomly assigned to erlotinib or platinum-based chemotherapy. Results of a planned interim analysis were presented at the 2011 American Society of Clinical Oncology (ASCO) meeting and subsequently published in the Lancet Oncology. **The objective response rate in erlotinib arm was 58%. Progression-free survival, the primary endpoint of the trial, was significantly increased with erlotinib compared with chemotherapy (median 10.4 versus 5.2 months, HR 0.37).** The difference in overall survival was not statistically significant, but more than 80 percent of patients initially treated with chemotherapy subsequently received an EGFR tyrosine kinase inhibitor. [35]

In the CALGB 30406 trials, erlotinib 150mg daily was compared to erlotinib 150mg daily with carboplatin AUC6 and paclitaxel 200mg/m2 as the first line therapy in never/light former smokers with advanced NSCLC. Overall 182 patients were randomized: 82 patients to erlotinib alone and 100 patients to erlotinib and chemotherapy. Over 80% of patients in the study were Caucasians and about 60% of them were women. In the subgroup of patients with EGFR mutation, **erlotinib alone resulted in objective response rate of 67%** with median PFS and OS of 15.7 and 37.3 months respectively. Addition of chemotherapy to erlotinib did not result in increase response rate, PFS or OS in EGFR mutated patients. [36]

Based on these and other trials, erlotinib or gefitinib monotherapy has become a standard first line therapy for stage IV patients with EGFR mutation. Erlotinib monotherapy is associated with 58-83% objective response rate in stage IV patients with EGFR mutations. This far exceeds the expected response rate from standard chemoradiation in stage III unselected NSCLC patients. The median progression free survival from erlotinib monotherapy in stage

IV disease with EGFR mutation is 10-13 months; similar to what we will normally achieved with standard chemoradiation in unselected patients with stage III NSCLC.

Rationale of Current Study:

The best management of patients with stage III NSCLC requires multidisciplinary approach. The current chemoradiation regimens have reached a plateau. A recent attempt to improve the outcome by increasing the dose of radiation has not been successful. Although the surgery and radiation offers a good local control, the big challenge in patients with stage III disease is systemic relapse. **A molecular agent that inhibits the development of systemic metastases for patients with stage III disease should be started as an initial therapy for the best outcome.** Based on the experience in advanced disease, the addition of a targeted therapy to a standard regimen is not always successful.

The EGFR mutated tumors form a subset of lung cancer that has significant responses from erlotinib and gefitinib. The response rate from erlotinib in stage IV patients with EGFR mutations were 67, 83 and 58% in CALGB 30406, OPTIMAL and EURTAC trials respectively.[33-36] These response rates far exceed the response rate seen with preoperative chemotherapy or chemoradiotherapy in stage III patients. The complete pathological responses have been described in patients with EGFR mutated stage IV disease who underwent resection of the primary tumors.[37]

The primary objective of this study is to estimate the rate of mediastinal nodal clearance after two months of neoadjuvant erlotinib in patients with stage III NSCLC with EGFR mutation. The mediastinal clearance is a robust measure of long term survival in patients with stage III NSCLC and will allow us to objectively evaluate effectiveness of the proposed regimen in short period of time. Rationale for correlative studies

Molecular and Cellular Determinants of erlotinib

Significant advances have been made over last several years in understanding both innate and acquired resistance to erlotinib in EGFR mutated tumors. Although several molecular or cellular basis for these resistance have been studied in pre-clinical models, these have not been validated in actual human specimens. Our study offers a great opportunity to examine some of these molecular markers in pre- and post-erlotinib specimen.

Recently it has been demonstrated that the polymorphisms in BIM protein are related to resistance to tyrosine kinase inhibitors including erlotinib. We plan also to examine BIM polymorphism from pre-erlotinib peripheral blood specimen our study. We will also plan to examine the BIM expression by immunohistochemistry in pre- and post erlotinib treated specimens. These data will be correlated with clinical and pathological response to validate BIM polymorphism and BIM-expression with complete pathological response and mediastinal down staging.

Recent studies have shown that more than half of the patients with acquired resistance to erlotinib have another mutation in exon 20 (T790M) conferring resistance to drug. Several studies have also shown that T790M mutation could present in pre-treatment specimen in about 30-35% of patients with erlotinib sensitive EGFR mutated tumors in low frequency. The theory of possible clonal selection by erlotinib in those patients is not very well validated. We plan to examine T790M mutation in both pre and post erlotinib specimens and correlate with complete pathological response and mediastinal downstaging.

EGFR mutated tumors also used alternative pathway particularly c-met/HGF pathway to circumvent EGFR inhibition. C-met and HGF overexpression has been associated with both innate and acquired resistance to erlotinib. We plan to examine baseline and post treatment c-met and HGF expression by IHC and correlate with response.

Autophagy as a mechanism of resistance to EGFR inhibition

Our recent work showed that erlotinib exposure induced autophagy in NSCLC cell lines. Autophagy is a self-protective mechanism that provides energy through the degradation and recycling of cytoplasmic contents and promotes cell survival. Autophagy has been shown to be a resistance mechanism to several chemotherapy and the proteosome inhibitors. Erlotinib exposure induced autophagy in both erlotinib resistance and sensitive cell lines. Inhibition of autophagy can be a potential mechanism to overcome the resistance to erlotinib. We plan to validate this finding examining autophagic markers (LC3-2 staining and electron microscopy (in limited number of patients)) in pre and post-erlotinb treated specimens.

Expression of Epithelial to Mesenchymal Transition (EMT) Markers and Sensitivity to Erlotinib

The expression of epithelial cell markers (such as E-cadherin, β-catenin) correlates with the sensitivity of NSCLC cells to erlotinib, whereas the loss of these epithelial cell markers expression and the expression of EMT markers (such as vimentin and/or fibronectin) correlate with resistance to erlotinib in *in vitro* and *in vivo* models [69, 70]. Furthermore, a small retrospective analysis of E-cadherin immunohistochemistry (IHC) expression on primary tumor samples from NSCLC patients suggests that the strong E-cadherin expression was associated with a significantly longer time to progression (n=28 and 37, respectively; hazard ratio, 0.37; log rank P=0.0028) and a nonsignificant trend toward longer survival with erlotinib plus chemotherapy treatment versus chemotherapy alone. We thus propose to determine the E-cadherin, vimentin and fibronectin expression by IHC in tumor specimens obtained from NSCLC patients enrolled in this study, and to correlate the level of expression with clinical efficacy.

Rash as a surrogate marker of clinical response and survival EGFR is expressed at high level in the skin and play a vital role in normal physiological function and the skin. Dysregulation of EGFR is implicated in psoriasis, although the mechanism is poorly

delineated and the good animal model for this disease is lacking. Treatments of all anti-EGFR therapeutic agents are associated with high incidence of skin changes (60-90%). Although most patients tolerate the rash well, severe skin rash is one of the dose-limiting toxicities and may lead to treatment interruption or discontinuation. Analysis of previous clinical studies suggested that the severity of rash correlates with survival in patients receiving erlotinib. Although the mechanisms for rashes are largely unknown, several ongoing studies are evaluating the relationship between skin and tumor EGFR expression, the relationship between the severity of skin rashes and clinical efficacy. Our unpublished data suggest that acute inflammatory reaction is present in the skin of mice that have received oral erlotinib treatment. However, the role of this acute inflammatory reaction in humans is not known.

3.0 PATIENT ELIGIBILITY:

3.1 Inclusion criteria

- Pathologically proven (either histologic or cytologic) diagnosis of Stage IIIA or IIIB non-small cell lung cancer; [according to AJCC Staging, 7th edition; see Appendix G] within 6 weeks of registration. The patient should have histologically or cytologically confirmed N2 disease.
- Activating mutation in *EGFR*
- No prior chemotherapy or radiation for lung cancer.
- Patients may be potentially resectable or unresectable.
- Stage III A or B disease, including no distant metastases- based on following diagnostic workup:
    - History/physical examination prior to registration.
    - CT Scan of the chest or PET Scan within 28 days of study entry
    - CT Scan of abdomen or MRI of abdomen or Pet Scan within 28 days of study entry
    - An MRI of the brain or Head CT Scan with contrast within 28 days of study entry
    - PET scan within 28 days of study entry
    - Mediastinoscopies are highly recommended.
- Patients must have measurable or evaluable disease.
- ECOG Performance Status 0-2.
- Age $\geq$ 18.
- CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:
    - Absolute neutrophil count (ANC) $\geq$1,500 cells/ul
    - Platelets $\geq$ 100,000 cells/ul
    - Hemoglobin $\geq$ 9.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb $\geq$ g/dl is acceptable.)
    - Serum creatinine $\leq$ 1.5 x ULN
    - Total bilirubin < 2.0 times the institutional Upper Limit of Normal (ULN)
    - AST and ALT $\leq$ 2.5 x the ULN
    - Women of childbearing potential must have:

- A negative serum or urine pregnancy test (sensitivity ≤ 25IU HCG/L) within 72 hours prior to the start of study drug administration
- Persons of reproductive potential must agree to use and utilize an adequate method of contraception throughout treatment and for at least 4 weeks after study drug is stopped prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

- Ability to take oral medication
- Patient must sign study specific informed consent prior to study entry.

3.2 Exclusion Criteria

- Pleural or pericardial effusion
  - Pleural effusions allowed if one of the following conditions are met: 1) Negative cytology after adequate sampling by thoracentisis 2) Effusion seen on CT scan but not on chest x-ray and deemed too small to tap under CT or ultrasound guidance
- Severe, active co-morbidity, defined as follows:
  - Cardiac Symptoms; any of the following should be considered for exclusion:
    - Uncontrolled angina, congestive heart failure or MI within (6 months)
    - Diagnosed congenital long QT syndrome
    - Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes)
    - Prolonged QTc interval on pre-entry electrocardiogram (> 450 msec)

  - History of significant bleeding disorder unrelated to cancer, including:
    - Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)
    - Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies)
    - Ongoing or recent (≤ 3 months) significant gastrointestinal bleeding

  - Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious) illness
  - Men and Women who:
    - are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for at least 4 weeks after cessation of study drug, or Women who:

- have a positive pregnancy test at baseline, or
- are pregnant or breastfeeding

4.0 TREATMENT:

4.1 Neoadjuvant erlotinib

Patients will be evaluated by a thoracic surgeon and medical and/or radiation oncologist and be determined to have either locally unresectable disease or potentially resectable disease.

Patients, who are eligible for the study, will be treated with preoperative/ neoadjuvant erlotinib 150 mg PO daily for two months.

Patients will be evaluated with repeat imaging studies (PET/CT or CT C,A,P) and will be evaluated for surgical resection. Patients who had progressive disease or are NOT a surgical candidate will come off the study and will be treated according to standard therapies. Patients may continue on erlotinib (off the study) if this is felt appropriate by the treating physicians. All patients will be followed up for progression free and overall survival.

4.2 Surgery

Patients who had significant clinical down staging and deemed medically fit to tolerate surgery will have surgical resection within 4-6 weeks after last staging imaging studies. Patients will continue on erlotinib until one day prior to surgical resection.

Patients with non-progressive disease who are not going for surgery should have mediastinal restaging done by either EUS/EBUS or mediastinoscopy.

The patient could receive either adjuvant chemotherapy, radiotherapy or both after surgical resection at the discretion of the treating physician. For the patients with unresectable, non-progressive disease, repeat mediastinal staging is required prior to proceeding with either chemotherapy, radiotherapy or both. Patients are also required to have repeat mediastinal evaluation even if the treating physician decides to continue on erlotinib beyond study duration.

4.2.1 Mediastinoscopy

A mediastinoscopy is highly recommended for all patients prior to neoadjuvant therapy for confirmation of mediastinal disease and also for tissue acquisition for EGFR mutation testing.

4.2.2 Pulmonary resection

Thoracotomy may be performed 4 weeks after neoadjuvant therapy. Surgery is performed if post neoadjuvant induction CT scan shows no significant progression of disease. Patients must be medically fit to tolerate surgery as deemed by the operative surgeon (post operative predicted FEV1> 40% predicted, no severe active comorbidity-see section 3). Complete surgical resection is the goal. This may entail pneumonectomy, bilobectomy, or lobectomy. Any procedure less than lobectomy is not recommended. Intraoperative frozen sections are performed at the discretion of the surgeon (bronchial resection margin is recommended). Reasons for incomplete resection will be documented. Bronchial stump coverage with local vascularized tissue is recommended.

4.2.3 Handling of mediastinal lymph nodes at thoracotomy

At the time of thoracotomy, mediastinal lymph node dissection is performed at the nodal station biopsied positive on prior mediastinoscopy. Either a full mediastinal lymph node dissection or mediastinal lymph node sampling is performed at all other lymph node stations at the discretion of the surgeon. For right sided lesions, this will include lymph node station 2, 4, 7, 8, 9, 10, and 11. Station 12 and 13 will be submitted along with the lung specimen. For left sided lesions, this will include lymph node station 5, 6, 7, 8, 9, 10, and 11. Station 12 and 13 will be submitted along with the lung specimen. On the left side, dissection or sampling of station 2 and 4 are at the discretion of the surgeon.

Proper documentation of mediastinal lymph node sampling in operative report is mandatory for the study. If the specific stations are not sampled, the reason should be documented in operative report. Failure to document mediastinal node sampling will be considered major protocol violation.

4.2.4 Operative complications

In hospital and 30 day morbidity and mortality will be prospectively monitored.

5.0 TOXICITIES, DOSE MODIFICATIONS, AND MANAGEMENT:

Adverse events should be coded according to CTCAE version 4 (Appendix C).[38]

5.1 Erlotinib Dose Modification/Toxicity Management

5.1.1 Dose Modifications

Discontinue Erlotinib (TARCEVA) for:

- Interstitial Lung Disease (ILD).

- Severe hepatic toxicity that does not improve significantly or resolve within three weeks
- Gastrointestinal perforation
- Severe bullous, blistering or exfoliating skin conditions.
- Corneal perforation or severe ulceration.

Withhold Erlotinib (TARCEVA):

- During diagnostic evaluation for possible ILD.
- For severe (CTCAE grade 3 to 4) renal toxicity, and consider discontinuation of TARCEVA.
- In patients without pre-existing hepatic impairment for total bilirubin levels greater than 3 times the upper limit of normal or transaminases greater than 5 times the upper limit of normal, and consider discontinuation of erlotinib (TARCEVA.).
- In patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline and consider discontinuation of erlotinib (TARCEVA)
- For persistent severe diarrhea not responsive to medical management (e.g., loperamide).
- For severe rash not responsive to medical management.
- For keratitis of (NCI-CTC version 4.0) grade 3-4 or for grade 2 lasting more than 2 weeks.
- For acute/worsening ocular disorders such as eye pain, and consider discontinuation of erlotinib (TARCEVA).

Reduce Erlotinib (TARCEVA) by 50 mg decrements:

- If severe reactions occur with concomitant use of strong CYP3A4 inhibitors [such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice] or when using concomitantly with an inhibitor of both CYP3A4 and CYP1A2 (e.g., ciprofloxacin). Avoid concomitant use if possible.
- When restarting therapy following withholding treatment for a dose-limiting toxicity that has resolved to baseline or grade ≤ 1.

Drugs Affecting Gastric pH

- Avoid concomitant use of erlotinib (TARCEVA) with proton pump inhibitors if possible. Separation of doses may not eliminate the interaction since proton pump inhibitors affect the pH of the upper GI tract for an extended period.
- If treatment with an H2-receptor antagonist such as ranitidine is required, erlotinib (TARCEVA) must be taken 10 hours after the H2-receptor antagonist dosing and at least 2 hours before the next dose of the H2-receptor antagonist.
- Although the effect of antacids on erlotinib pharmacokinetics has not been evaluated, the antacid dose and the erlotinib (TARCEVA) dose should be separated by several hours, if an antacid is necessary.

6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR:

6.1 Schedule of Evaluations

Parameter	Pre-study	Neoadjuvant Erlotinib Q 2wks*** (D1,15,29,43)	Neoadjuvant Erlotinib (D57)	Surgery (within 4-6 weeks from PET/CT scan)	Post-Surgical Follow up[h]	End of Treatment Visit	FU**
History	X	X	X		X		X
Physical examination	X	X	X		X	X	X
Weight	X	X	X		X	X	X
Vital signs	X	X	X		X	X	X
Performance status (ECOG)	X	X	X		X	X	X
CBC, differential, platelet count	X	X	X		X	X	X
, LFTs, Cal, Mg, [A]	X	X	X		X	X	X
Serum HCG [A]	X						
PFTs[B]	X						
AE Evaulation		X	X		X	X	
CT scan chest or total body PET/CT Scan **and** CT Scan or MRI of Abdomen or total body PET/CT Scan[c]	X		X				Every six month for first year then yearly till 5 years
PET/CT Scan[d]	X		X				
MRI of Brain or CT of Head with contrast [*]	X		If clinically indicated				If clinically indicated
Mediastinoscopy/ EUS/EBUS [g]	X		If clinically indicated##				
Surgical Evaluation	X		X				
Operative & Surgical pathology report					X		
Perioperative morbidity form					X		
EKG [f]	X						
Pill diary		X	X				

[A] -Pre-enrollment laboratory tests should be performed within 14 days of study entry. HCG is required only for patients who are women with childbearing potential and must be done within 72 hours prior to start of study drug administration.

[B]- PFTs within 8 weeks of study entry

[C]- CT Scan of the chest or Pet Scan within 28 days of study entry and a CT Scan or MRI of abdomen through the Liver within 28 days of study entry

*An MRI of the brain with contrast or Head CT Scan within 28 days of study entry

[d]-PET/CT scan within 6 weeks of study entry is highly recommended and required for operable patients. If a PET scan is performed then a bone scan is not required.
[f]- EKG within 6 weeks of study entry.
[g]- Mediastinoscopies are highly recommended for documentation of N2 disease. EUS or EBUS may substitute mediastinoscopy in appropriate clinical setting.
h- Subjects who do not receive surgery will have an end of treatment visit 30 days (±3 days) after Post-Treatment Visit.

**Follow for survival and recurrence every 3 months for first year, every 6 months afterward and document on follow up form.
*** specified dates +/- 2 working days
required for patients with non-progressive disease NOT undergoing surgery.

7.0 RESPONSE ASSESSMENT:

7.1 Eligibility

RECIST 1.1 will be used for tumor measurements after neoadjuvant erlotinib.[41]

Only patients with measurable or evaluable disease at baseline will be included:

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. 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.

- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

7.2 Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

7.3 Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.4 Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the 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
* 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

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

7.5 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

8.0 CORRELATIVE STUDIES:

Informed consent must be signed prior to obtaining and/or submission of any materials for the laboratory correlative studies.

8.1 Statement of Hypotheses and Objectives:

The objective of the correlative studies is to identify molecular and cellular makers in the tumor and the skin that will predict either a response or resistance to erlotinib in EGFR mutated tumors. We plan to identify the molecular markers that will predict the rate of mediastinal nodal clearance in stage III NSCLC patients with EGFR mutation.

Based on the literature and our preliminary data, we hypothesize that:

1) The polymorphism and baseline BIM expression will predict a response to erlotinib

2) Baseline c-met expression and the presence of T790M mutation in pre-treatment tumor specimens will predict resistance to erlotinib

3) We expect to see autophagy induction in post-treatment specimens compare to pre-treatment specimens. We plan to correlate the baseline autophagy with either sensitivity or resistance to erlotinib

4) The expression of Epithelial to Mesenchymal Transition (EMT) Markers and sensitivity to erlotinib.

5) The presence of ≥ grade 2 skin changes is associated with erlotinib-associated inhibition of pEGFR and immune and inflammatory changes in the skin, which correlate with clinical response and patient survival to erlotinib.

6) Patients who develop significant skin rashes have more competent T-cell mediated immunity that correlate with better clinical outcome.

8.2 Background and Rationale (see section 2.0).

8.3 Tissue Requirements and Assays

Although high throughput techniques like microarray and proteomics will allow simultaneous determination of up to thousands of genes and proteins in patients before and after the treatment, it is limited by the need for large amounts of tumor tissues and labored collection. Thus, we will focus on several biomarkers suggested by our and others preclinical studies for erlotinib to predict their clinical response and benefit, and only performed array-based genomic analysis and proteomics in selected patients.

8.3.1 Tissue requirements:

Tumor samples: We will put all efforts to obtain at least the diagnostic tissue blocks for the correlative studies. Tumor tissues will be available from the diagnostic biopsy. Pre- and post-treatment tumor biopsies will be obtained in available patients. The tumors will be embedded in OCT solution or snap frozen in a liquid nitrogen bath. Aliquots of tumors will be fixed in formalin and embedded in paraffin.

Skin samples: Serial 3mm-punch skin biopsies under local anesthesia on the back of upper torso are minimal invasive and can be done within 20 minutes during an outpatient visit. This is required only for all patients enrolled in the study who consent to the biopsy, with or without the presence of grade 2 or above skin rash after initiation of erlotinib. A separate or immediate after clinic visit with the treating physician might be arranged to perform the skin biopsy as needed. These samples (~400 mg) will be snapped frozen immediately in liquid nitrogen, and embedded in paraffin.

Timing of tumor or skin biopsy: Pre-treatment biopsy could be obtained within 2 weeks before initiation of the drug treatment. The onset of skin rashes is usually two weeks in patients and last for at least 24 hours after last dose of erlotinib, Thus we will perform post-treatment skin biopsy during the planned surgical resection for lung cancer OR at the peak of skin rash as per patient and treating physician's discretion.

8.3.2 Tissue resources:

The following tissue resources are allowed to collect tissue samples at the time of initial diagnosis, pre- and post-treatment.

8.3.2.1 Formalin-fixed, paraffin-embedded (FFPE) tumor blocks
8.3.2.2 Endobronchial brush and wash
8.3.2.3CT-guided core biopsy of tumor
8.3.2.4 Punch biopsy of skin
8.3.2.5 Peripheral blood

8.3.3 The following assays will be performed:

1. Histological Evaluation
2. DNA isolation and mutational analysis
3. FISH
4. Tissue microarray (TMA) and Immunohistochemistry (IHC)
5. ELISPOT assay

Histological Evaluation: Specimens will be evaluated by routine hematoxylin and eosin (H&E) stain for the following assessments: 1) percentage of variable tumor; and 2) non-neoplastic adjacent normal tissue.

DNA Isolation and Mutational Analyses: Tumor cells will be isolated on sections from FFPE tissue blocks by macrodissection if the slides consist of more than 75% of tumor. If the slides consist of less than 75% of tumor, we will first isolate tumor cells from normal cells on the slide onto a thin polymer film (CapSure LCM Caps, Arcturus, Mountain View, CA) by a PixCell IIe Laser Capture Microdissection (LCM) System (Arcturus, Mountain View, CA). The tumor cells will be dissociated from the film in proteinase K-containing lysis buffer. The 75% is chosen arbitrarily. Our previous experience reveals that we can detect a heterozygous point mutation by direct sequencing if it is present at least at 15% (data not shown). An estimate of 3,000 to 10,000 laser shots using a laser beam of 7.5-μm diameter will be needed to obtain enough analyzable DNA for at least 10 PCR reactions. As normal controls, DNA isolated from adjacent normal lung tissues either by LCM or by macrodissection (if normal tissues is >75%) will be used.

Genomic DNA will be isolated from tumor samples by the DNeasy tissue kit (Qiagen). Targeted gene segments will be amplified by PCR and the mutation status will be determined by the standard procedures.

Tissue Microarray: The development of tissue arrays allows the evaluation of each of many proteins in many sets of normal and tumor tissues using a single slide for each probe. It provides a powerful way to follow up the candidate protein changes proposed in this study with control of technical variation. We will determine the changes in protein expression on tissue microarray (TMA) by IHC and correlate these altered protein changes with the clinical response to erlotinib. Five-μm sections of normal and tumor tissues embedded in paraffin will be stained with H&E to identify morphologically

representative area of normal and tumor tissues, from which core biopsies will be taken. The tissue microarray will be done with the Tissue Arrayer (Beecher Instruments, Silver Spring, MD). From each specimen (donor), tissue cores with a diameter of 0.6 or 1.0 mm are punched and arrayed on a blank paraffin block (recipient). The spacing between the centers of two adjacent specimens on the array ranged from 3 mm to 8 mm. Two to three hundred cores could be created within the array block. Then the recipient block is incubated at 37^0C oven for 1 hour to soften the paraffin and melt the surface of the block.

Immunohistochemistry (IHC): Tissue arrays containing diagnostic, pre- and post-treatment tumor and normal human NSCLC tissues (as described above) will be cut in 5-µm sections, deparaffinized, rehydrated, and quenched with 1.5% H_2O_2. For EGFR studies, the slides will be treated with DakoCytomation Target Retrieval Solution (DAKO, Carpinteria, CA) in a steam bath at 95°C for 45 minutes. After equilibration in PBS for 15 minutes, the slides were placed in an autostainer (DAKO, Carpinteria, CA) and stained with antibodies to EGFR (DAKO; 1:100 dilution). Immunoreactivity will be detected using DAKO EnVision methods (DAKO) according to the manufacturer recommended procedures. The activated EGFR is detected using antibodies against the phosphorylated forms of EGFR (p-EGFR). Similar IHC staining will be performed using with antibodies specific for other proteins as described previously.[88] For negative controls, slides will be treated with the same procedure, including antigen retrieval, except for omission of the primary antibodies. The level of expression will be assessed as percentage of positive staining cells, and scored as 0 (0%), +1 (1-25%), +2 (26-50%) and +3 (51-100%) as described before [89]. Cell pellets from human NSCLC cell lines known to be positive or negative for EGFR will be used as positive or negative controls for EGFR expression. Negative controls will also be performed by omission of the primary antibody. A sample of recording IHC results is illustrated in Appendix I.

Human IFN-γ ELISA: We will collect 5 ml of peripheral blood using citrate, EDTA, or heparin as anticoagulant from the patients before and 2 weeks after treatment. Plasma will be collected by centrifuging the blood for 10 minutes at 1000 x g within 20 minutes of collection. The plasma will be stored at ≤ 20°C or shipped on dry ice. We will analyze the patient plasma samples for in vitro T-cell function by ELISPOT assay using tumor specific antigens. A positive interferon gamma (IFN-γ) response to a common antigen (such as whole influenza virus or EBV) will be used as a control. The results will be correlated to the skin changes and clinical outcome of the patients.

9.0 PATIENT REGISTRATION:

All patients will be registered through the Clinical Trials Office at Montefiore Medical Center (Telephone: 718-379-6861) Monday through Friday 9:00am – 5:00pm Eastern Standard Time. Eligibility Checklist and Registration Form with supporting documentation, and the signed Patient Consent Form must be emailed to the clinical trials office at Montefiore Medical Center, cpdmu-registration@montefiore.org , at the time of registration and prior to patient treatment. Please copy the Montefiore Study and Regulatory Coordinator on this email, as well as the Principal Investigator at Montefiore. E-mail addresses are available at the cover sheet of this protocol document.

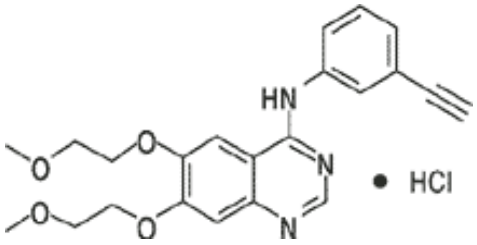
At the time of registration, all eligibility criteria must be checked. Patients must meet all of the eligibility requirements listed in Appendix B (Eligibility Checklist) (Section 3.0). Patients must not start protocol treatment prior to registration.

It is the treating physician's responsibility to review all data submitted to the Clinical Trials Office for accuracy and completeness and he/she must sign the off study form.

10.0 PHARMACEUTICAL INFORMATION

10.1 Erlotinib (Tarceva®)

Chemical Name: Erlotinib is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. TARCEVA® contains erlotinib as the hydrochloride salt, which has the following structural formula:



Other Names: CP-358, 774, USAN: OSI-774 (Erlotinib) hydrochloride, Tarceva®

Classification: Signal Transduction Inhibitor, Tyrosine kinase Inhibitor (EGFR)

Molecular Formula: $C_{22}H_{23}N_3O_4.HCl$ **Molecular Weight**: 429.90

Mode of Action:
The mechanism of clinical anti-tumor action of erlotinib is not fully characterized. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surface of normal cells and cancer cells.

How Supplied:
Erlotinib tablets are available in 25 mg, 100 mg and 150 mg erlotinib and contain the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. All tablets are round, white, film-coated bi-convex tablets without markings. Erlotinib hydrochloride, clinical trial material will be provided by Astellas, the study sponsoe.

Storage:
The intact bottles should be stored at controlled room temperature15°C-30°C-(59°F and 86°F). Tarceva® tablets are supplied in blue-white high-density polyethylene (HDPE) bottles of 30 each with some overage.

Route of Administration: Oral.

Method of Administration
Tarceva® tablets should be taken at approximately the same time each day. Each Tarceva® dose is to be taken with up to 200 mL (~ 1 cup or 8 oz) of water one hour before or two hours after meals or medications, including vitamins and iron supplements. Tarceva® should not be taken with grapefruit juice. The entire dose must be taken at one time. If the patient vomits after taking the tablet(s), the dose is replaced only if the tablet(s) can actually be seen and counted.

Warnings and Precautions

Interstitial Lung Disease (ILD):

Cases of serious ILD, including fatal cases, can occur with TARCEVA treatment. The overall incidence of ILD in approximately 32,000 TARCEVA-treated patients in uncontrolled studies and studies with concurrent chemotherapy was approximately 1.1%. In patients with ILD, the onset of symptoms was between 5 days to more than 9 months (median 39 days) after initiating TARCEVA therapy. Withhold TARCEVA for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever pending diagnostic evaluation. If ILD is confirmed, permanently discontinue TARCEVA

Renal Failure

Hepatorenal syndrome, severe acute renal failure including fatal cases, and renal insufficiency can occur with TARCEVA treatment. Renal failure may arise from exacerbation of underlying baseline hepatic impairment or severe dehydration. The pooled incidence of severe renal impairment in the 3 monotherapy lung cancer studies was 0.5% in the TARCEVA arms and 0.8% in the control arms. The incidence of renal impairment in the pancreatic cancer study was 1.4% in the TARCEVA plus gemcitabine arm and 0.4% in the control arm. Withhold TARCEVA in patients developing severe renal impairment until renal toxicity is resolved. Perform periodic monitoring of renal function and serum electrolytes during TARCEVA treatment.

Hepatotoxicity with or without Hepatic Impairment

Hepatic failure and hepatorenal syndrome, including fatal cases, can occur with TARCEVA treatment in patients with normal hepatic function; the risk of hepatic toxicity is increased in patients with baseline hepatic impairment. In clinical studies where patients with moderate to severe hepatic impairment were excluded,

the pooled incidence of hepatic failure in the 3 monotherapy lung cancer studies was 0.4% in the TARCEVA arms and 0% in the control arms. The incidence of hepatic failure in the pancreatic cancer study was 0.4% in the TARCEVA plus gemcitabine arm and 0.4% in the control arm. In a pharmacokinetic study in 15 patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 of these 15 patients died within 30 days of the last TARCEVA dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin > 3 x ULN.

Perform periodic liver testing (transaminases, bilirubin, and alkaline phosphatase) during treatment with TARCEVA. Increased frequency of monitoring of liver function is required for patients with pre-existing hepatic impairment or biliary obstruction. Withhold TARCEVA in patients without pre-existing hepatic impairment for total bilirubin levels greater than 3 times the upper limit of normal or transaminases greater than 5 times the upper limit of normal. Withhold TARCEVA in patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline. Discontinue TARCEVA in patients whose abnormal liver tests meeting the above criteria do not improve significantly or resolve within three weeks.

Gastrointestinal Perforation

Gastrointestinal perforation, including fatal cases, can occur with TARCEVA treatment. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease may be at increased risk of perforation. The pooled incidence of gastrointestinal perforation in the 3 monotherapy lung cancer studies was 0.2% in the TARCEVA arms and 0.1% in the control arms. The incidence of gastrointestinal perforation in the pancreatic cancer study was 0.4% in the TARCEVA plus gemcitabine arm and 0% in the control arm. Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation.

Bullous and Exfoliative Skin Disorders

Bullous, blistering and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal, can occur with TARCEVA treatment. The pooled incidence of bullous and exfoliative skin disorders in the 3 monotherapy lung cancer studies was 1.2% in the TARCEVA arms and 0% in the control arms. The incidence of bullous and exfoliative skin disorders in the pancreatic cancer study was 0.4% in the TARCEVA plus Gemcitabine arm and 0% in the control arm. Discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions.

Myocardial Infarction/Ischemia

In the pancreatic carcinoma trial, six patients (incidence of 2.1%) in the TARCEVA/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, 3 patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.1%), and one died due to myocardial infarction. The pooled incidence of myocardial infarction/ischemia in the 3 monotherapy lung cancer studies was 0.2% in the TARCEVA arms and 0.4% in the control arms.

Cerebrovascular Accident

In the pancreatic carcinoma trial, seven patients in the TARCEVA/gemcitabine group developed cerebrovascular accidents (incidence: 2.5%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents. The pooled incidence of cerebrovascular accident in the 3 monotherapy lung cancer studies was 0.6% in the TARCEVA arms and 0.9% in the control arms.

Microangiopathic Hemolytic Anemia with Thrombocytopenia

The pooled incidence of microangiopathic hemolytic anemia with thrombocytopenia in the 3 monotherapy lung cancer studies was 0% in the TARCEVA arms and 0.1% in the control arms. The incidence of microangiopathic hemolytic anemia with thrombocytopenia in the pancreatic cancer study was 1.4% in the TARCEVA plus gemcitabine arm and 0% in the control arm.

Ocular Disorders

Corneal perforation or ulceration can occur with TARCEVA treatment. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with TARCEVA treatment and are known risk factors for corneal ulceration/perforation. The pooled incidence of ocular disorders in the 3 monotherapy lung cancer studies was 17.8% in the TARCEVA arms and 4% in the control arms. The incidence of ocular disorders in the pancreatic cancer study was
12.8% in the TARCEVA plus gemcitabine arm and 11.4% in the control arm. Interrupt or discontinue TARCEVA therapy if patients present with acute/worsening ocular disorders such as eye pain

Hemorrhage in Patients Taking Warfarin

Severe and fatal hemorrhage associated with International Normalized Ratio (INR) elevations can occur when TARCEVA and warfarin are administered

concurrently. Regularly monitor prothrombin time and INR during TARCEVA treatment in patients taking warfarin or other coumarin-derivative anticoagulants

Embryo-Fetal Toxicity

Based on its mechanism of action, TARCEVA can cause fetal harm when administered to a pregnant woman. When given during organogenesis, erlotinib administration resulted in embryo-fetal lethality and abortion in rabbits at doses approximately 3 times the recommended human daily dose of 150 mg. If TARCEVA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 2 weeks after the last dose of TARCEVA. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TARCEVA.

ADVERSE REACTIONS

The following serious adverse reactions, which may include fatalities, are discussed in greater detail above:

- Interstitial Lung Disease (ILD) Renal Failure
- Hepatotoxicity with or without Hepatic Impairment
- Gastrointestinal Perforation
- Bullous and Exfoliative Skin Disorders
- Myocardial Infarction/Ischemia
- Cerebrovascular Accident
- Microangiopathic Hemolytic Anemia with Thrombocytopenia
- Ocular Disorders
- Hemorrhage in Patients Taking Warfarin

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety evaluation of TARCEVA is based on more than 1200 cancer patients who received TARCEVA as monotherapy, more than 300 patients who received TARCEVA 100 or 150 mg plus gemcitabine, and 1228 patients who received TARCEVA concurrently with other chemotherapies.

The most common adverse reactions with TARCEVA are rash and diarrhea usually with onset during the first month of treatment. The incidences of rash and

diarrhea from clinical studies of TARCEVA for the treatment of NSCLC and pancreatic cancer were 70% for rash and 42% for diarrhea.

Non-Small Cell Lung Cancer

First-Line Treatment of Patients with EGFR Mutations

The most frequent (≥ 30%) adverse reactions in TARCEVA-treated patients were diarrhea, asthenia, rash, cough, dyspnea and decreased appetite. In TARCEVA-treated patients the median time to onset of rash was 15 days and the median time to onset of diarrhea was 32 days.

The most frequent Grade 3-4 adverse reactions in TARCEVA-treated patients were rash and diarrhea. Dose interruptions or reductions due to adverse reactions occurred in 37% of TARCEVA-treated patients, and 14.3% of TARCEVA treated patients discontinued therapy due to adverse reactions. In TARCEVA-treated patients, the most frequently reported adverse reactions leading to dose modification were rash (13%), diarrhea (10%), and asthenia (3.6%).

Selected, common adverse reactions in the study, occurring in at least 10% of patients who received TARCEVA or chemotherapy and an increase in ≥ 5% in the TARCEVA treated group, are summarized by NCI-CTC (version 3.0) Grade in Table 1. The median duration of TARCEVA treatment was 9.6 months in the study 4.

Table 1: Selected Adverse Reactions with an Incidence Rate ≥ 10% and an Increase of ≥ 5% in the TARCEVA-treated Group

	TARCEVA N = 84		**Chemotherapy † N = 83**	
MedDRA Preferred Term	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Rash ‡	85	14	2	0
Diarrhea	62	5	21	1
Cough	48	1	40	0
Dyspnea	45	8	30	4
Dry skin	21	1	2	0
Back pain	19	2	5	0
Chest pain	18	1	12	0
Conjunctivitis	18	0	0	0
Mucosal inflammation	18	1	6	0
Pruritus	16	0	1	0
Paronychia	14	0	0	0
Arthralgia	13	1	6	1
Musculoskeletal pain	11	1	1	0

DRUG INTERACTIONS

CYP3A4 Inhibitors
Erlotinib is metabolized predominantly by CYP3A4. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 67%. When TARCEVA was

co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure [AUC] and maximum concentration [Cmax] increased by 39% and 17%, respectively. Dose modifications are recommended.

CYP3A4 Inducers

Pre-treatment with the CYP3A4 inducer rifampicin for 7-11 days prior to TARCEVA decreased erlotinib AUC by 58% to 80%. Dose modifications are recommended

Drugs Affecting Gastric pH

Co-administration of TARCEVA with omeprazole decreased erlotinib AUC by 46% and co-administration of TARCEVA with ranitidine 300 mg decreased erlotinib AUC by 33%. When TARCEVA was administered with ranitidine 150 mg twice daily (at least 10 h after the previous ranitidine evening dose and 2 h before the ranitidine morning dose), erlotinib AUC decreased by 15%. Increasing the dose of TARCEVA when co-administered with such agents is not likely to compensate for the loss of exposure. Scheduling modifications are recommended

Cigarette Smoking

Cigarette smoking results in reductions in erlotinib AUC. Dose modifications are recommended

Anticoagulants

Interaction with coumarin-derived anticoagulants, including warfarin, leading to increased International Normalized Ratio (INR) and bleeding adverse reactions, which in some cases were fatal, have been reported in patients receiving TARCEVA. Regularly monitor prothrombin time or INR in patients taking coumarin-derived anticoagulants. Dose modifications of TARCEVA are not recommended

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

Risk Summary

Based on its mechanism of action, TARCEVA can cause fetal harm when administered to a pregnant woman. When given during organogenesis, erlotinib administration resulted in embryo-fetal lethality and abortion in rabbits at doses approximately 3 times the recommended human daily dose of 150 mg. If TARCEVA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Animal Data

Erlotinib has been shown to cause maternal toxicity resulting in embryo-fetal lethality and abortion in rabbits when given during the period of organogenesis at doses that result in plasma drug concentrations approximately 3 times those achieved at the recommended dose in humans (AUCs at 150 mg daily dose). During the same period, there was no increase in the incidence of embryo-fetal lethality or abortion in rabbits or rats at doses resulting in exposures approximately equal to those in humans at the recommended daily dose. In an independent fertility study female rats treated with 30 mg/m2/day or 60 mg/m2/day (0.3 or 0.7 times the recommended daily dose, on a mg/m2 basis) of erlotinib had an increase in early resorptions that resulted in a decrease in the number of live fetuses.

No teratogenic effects were observed in rabbits or rats dosed with erlotinib during organogenesis at doses up to 600 mg/m2/day in the rabbit (3 times the plasma drug concentration seen in humans at 150 mg/day) and up to 60 mg/m2/day in the rat (0.7 times the recommended dose of 150 mg/day on a mg/m2 basis).

Nursing Mothers

It is not known whether erlotinib is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from TARCEVA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of TARCEVA in pediatric patients have not been established.

Geriatric Use

Of the 1297 subjects in clinical studies of TARCEVA for the treatment of NSCLC and pancreatic cancer 40% were 65 and older while 10% were 75 and older. No overall differences in safety or efficacy were observed between subjects 65 years and older and those younger than 65.

Females and Males of Reproductive Potential

Contraception

Females
Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential to use highly effective contraception during treatment with TARCEVA, and for at least 2 weeks after the last dose of TARCEVA. Advise patients to

contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TARCEVA.

Patients with Hepatic Impairment

Patients with hepatic impairment (total bilirubin > upper limit of normal (ULN) or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN

In vitro and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver. However, erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases.

Patients with Renal Impairment

Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

OVERDOSAGE

Single oral doses of TARCEVA up to 1,000 mg in healthy subjects and weekly doses up to 1,600 mg in cancer patients have been tolerated. Repeated twice-daily doses of 200 mg single-agent TARCEVA in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, an unacceptable incidence of severe adverse reactions, such as diarrhea, rash, and liver transaminase elevation, may occur above the recommended dose In case of suspected overdose, TARCEVA should be withheld and symptomatic treatment instituted.

Availability:

Tarceva® (Erlotinib) is commercially available and is not currently approved for neoadjuvant treatment but it has indication for the first line of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test; as the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy and for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. In the U.S., Tarceva® (Erlotinib) is marketed by both Genentech BioOncology and Astellas. Clinical trial material that is “commercial in nature” will be provided by Astellas

References

Investigator’s Brochure: OSI 774 (Erlotinib, Tarceva®) Edition 17, dated 21 Mar 2013.

11.0 AGENT ACCOUNTABILITY:

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from manufacturer using a Drug Accountability Record Form.

12.0 REGULATORY AND REPORTING REQUIREMENTS:

12.1 Definitions

An adverse event can occur on any clinical trial; it is the responsibility of the Principal Investigator and his/her research team to identify, review and report all necessary adverse events to the institutional IRB, the sponsor and governmental agencies (i.e., NCI and/or FDA) as appropriate. Adverse events should be identified through standard, routine protocol review and clinical assessment of each subject participating in the clinical trial. This review should be timely in order to meet the requirements for adverse event reporting defined below.

An adverse event An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of erlotinib whether or not considered related to erlotinib.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

Adverse events (AEs) will use the descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix C). A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6 (Pharmaceutical Information). The reported procedures to be followed are presented in the investigators' brochures.

In the context of multicenter clinical trials, Adverse Events can be characterized as either internal adverse events or external adverse events. From the perspective of one particular institution engaged in a multicenter clinical trial, internal adverse events are those adverse events experienced by subjects enrolled by the investigator(s) at that institution,

whereas external adverse events are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all Adverse Events would be considered internal adverse events.

Unanticipated Problem

Any event, deviation, or problem that meets ALL of the following criteria:

- unexpected; AND
- possibly, probably or definitely related to study participation; AND fatal, life-threatening, or serious OR suggests greater risk of harm to study
- participant(s)or others than was previously known or recognized.

Unexpected

An event can be categorized as unexpected if it occurs in one or more subjects participating in a research protocol; and the nature, severity, or frequency of which is not consistent with either:

i. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in protocol-related documents such as: the IRB-approved research protocol; any applicable investigator brochure: the current IRB-approved informed consent document; or other relevant sources of information, such as product labeling and package inserts; or
ii. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Serious Adverse Event (SAE)

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

i. death,
ii. a life-threatening adverse reaction,
iii. inpatient hospitalization or prolongation of existing hospitalization,
iv. persistent or significant incapacity or substantial disruption of the ability to
v. conduct normal life functions, or
vi. a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

12.2 Determination of reporting requirements

Reportable Events

Any event that meets the definition of an Unanticipated Problem must be reported to the IRB within 5 business days. For multicenter studies, this would include such events that occur at external sites.

Other events that must be reported to the IRB include:

- The death of a participant in a "greater-than-minimal-risk" protocol being conducted at a site under the jurisdiction of the Einstein IRB, even if "anticipated", if it occurs within 30 days of a study-related procedure or the administration of a study drug.
- A Protocol Deviation that may place the participant or others at greater medical, physiological, social risk or economic risk than was previously known or recognized.
- Any deviation from IRB or Institutional Policy or Procedure which has the potential to adversely impact one or more subject or the overall integrity of data collected.
- Any reporting the PI is required to report directly to the FDA (e.g. the PI is the sponsor- Investigator, a protocol involving the use of an HUD).
- Any incident, experience, or outcome that indicates that the participant or others were placed at greater medical, physiological, social risk or economic risk than was previously known or recognized.
- Any reporting that the IRB cites as a condition of approval of the protocol.
- Complaint from a participant or other individual when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Deviation from the IRB Informed Consent Policy.
- Systematic data collection errors.
- Breach of confidentiality.
- Any action taken to eliminate an apparent immediate hazard to a research subject.
- Incarceration of a research subject.
- Sponsor or regulatory audit that requires corrective action.
- Suspension or restriction of an Investigator's clinical professional license.
- Disqualification or suspension of the Investigator by the FDA, NIH or other agency.

A record of non-reportable events and deviations must be maintained by the PI in a log and for greater than minimal risk studies must be submitted to the IRB as part of the annual review of the protocol. Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

Reporting requirements may include the following considerations:

1) whether the patient has received an investigational or commercial agent;
2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event
3) the phase (1, 2, or 3) of the trial
4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND) (5-AZA). In some instances, the investigational agent may be

available commercially, but is actually being tested for indications not included in the approved package label.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: ***Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0***. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed.

Step 2: *Grade the event using the NCI CTCAE*.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is **NOT** listed in section 6.5. the current NCI Agent-Specific Adverse Event List for the investigational agent.

Step 5: *Review the "Additional instructions, requirements, and exceptions for this protocolspecific requirements for expedited reporting of specific adverse events that require specialmonitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents*.

NOTE: If the patient received at least one dose of investigational agent, follow the guidelines for investigation agents. If no investigational agent was administered, follow the guidelines for non-investigational agents.

12.3 Reporting methods

Any event that meets the definition of an Unanticipated Problem must be reported to the Montefiore-Einsetin IRB within 5 business days. The Unanticipated Problem Report Form can be found on the Einstein IRB website: http://einstein.yu.edu/administration/institutional-review-board/forms.aspx. All Reportable Events must be submitted to the IRB within 5 business days of the identification of the event by the research staff. Only the Principal Investigator may sign off on reportable event submissions, although any member of the research team may initiate the report. A record of non-reportable events and deviations must be maintained

by the PI in a log and for greater than minimal risk studies must be submitted to the IRB as part of the annual review of the protocol.

For events that are deemed reportable at participating sites, a copy of the reportable event must be submitted to Montefiore Medical Center within 2 business days. You may send to the Principal Investigator and the Study Coordinator. All contact information is located at the cover page of this document. If not reportable, Adverse Events should be logged in the CRF page, and any non-reportable serious and/or unanticipated adverse events should be logged on the Adverse Event Log provided by Montefiore for review at the Montefiore Data Safety Monitoring Committee meetings and during IRB annual review.

Montefiore will submit all reportable events to Astellas Drug Safety within 5 business days by submitting to: Astellas Drug Safety: safety-US@astellas.com OR Fax number: 847-317-1421.

12.4 Trial Monitoring

This trial will be monitored by the Albert Einstein Cancer Center Data Safety Monitoring Committee (AECC DSMC). A copy of the monitoring plan is maintained at the CPDMU**.** The DSMC as part of its function performs quarterly reviews of Clinical Trials Compliance Audits, monthly reviews Adverse Events Reports, and monthly reviews of internally monitored Phase I/Phase II trials for accrual and response. Other monitoring activities are established as necessary in a protocol specific manner**.**

This trial will be part of the monthly Quality Assurance Audits. Each patient will be evaluated within 8 weeks of registration. This permits evaluation of consent, eligibility, and treatment/dose modification/Adverse Event (AE) reporting, and data quality for the first cycle (or month) of treatment. Patients at participating sites are evaluated for eligibility and consent at the time of registration by clinical and administrative staff.

This trial may also be eligible for quarterly Quality Enhancement Audit. Each audit consists of a review of regulatory documents, pharmacy drug accountability (if applicable) and patient case review, confirming eligibility, protocol compliance and source documentation

The results of the audit will be presented at the following month's DSMC meeting. The DSMC has the authority to close trial to patient accrual should the risk to patients be excessive or results require a corrective plan from the Principal Investigator. All study suspensions and closures will be forwarded to the IRB and study sponsor. All audit reports are forwarded to the DSMC and presented to the DSMC by the Audit Committee Coordinator.

12.5 Expedited reporting for investigational agents

Follow guidelines in section 12.2 regarding criteria that required expedited reporting.

For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Sections 12.2 must be reported on an expedited adverse event report form as per guidelines in section 12.2

Adverse events that require expedited reporting are outlined below: for the investigational agent erlotinib.

The following be reported as a SAE:

- **Grade 2 (moderate) and Grade 3 (severe) Events** – Only events that are Unexpected AND Possibly, Probably or Definitely Related/Associated with the Intervention.

- **ALL Grade 4 (life threatening or disabling) Events** – Unless expected AND specifically listed in protocol as not requiring reporting.

- **ALL Grade 5 (fatal) Events** – When participant is enrolled and actively participating in the trial OR when event occurs within 30 days of the last study intervention.

Additional instructions, requirements and exceptions for this protocol::

With respect to determining the specific day by which the event must be reported, the day the reporter learns of the adverse event constitutes "Day 0".

12.6 Responsibilities of participating sites

Serious adverse events will be reported to each participating institution according to protocol guidelines and local policies and procedures governing the local Institutional Review Board.

A copy of all SAE's should be faxed to the Coordinating Center, Montefiore Medical Center (see cover page) within two (2) business days by the participating site. Other events that should be reported include: (1) any pregnancy occurring in association with use of erlotinib, and (2) any new information regarding any SAE.

12.7 Responsibilities of the Coordinating Center (Montefiore Medical Center) and Astellas.

The Coordinating Center (Montefiore Medical Center) will maintain records and

provide reports to Astellas for the following Adverse Experiences: (1) all serious, unexpected, adverse events, (2) any significant increase in the frequency of serious expected adverse events, and (3) an annual progress report including number of patients accrued, date on study, date off study, vital status (alive/dead and date alive/dead).

13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY:

Extraordinary medical circumstances or withdrawal of consent by the patient:

If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

1. **Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.**
2. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
3. The physician feels it is in the best interest of the patient to stop the treatment.
4. Inter current illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
5. Non protocol chemotherapy or immunotherapy is administered during the study
6. Noncompliance with protocol or treatment—major violation
7. Suspected Pregnancy
8. Patient is lost to follow-up
9. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
10. Death

In this event notify:

Study PI (contact information on cover page of protocol)
Study Coordinator(contact information on cover page of protocol)
Regulatory Coordinator(contact information on cover page of protocol)
Clinical Trials Office: Phone:**718-379-6861** AND e-mail:
cpdmu-registration@montefiore.org

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival with follow-up forms as dictated by the protocol**

14.0 FOLLOW-UP:

Subjects who undergo surgery will have a post-surgery follow-up visit 30 days (±3 days) after surgery. Subjects who do not receive surgery will have an end of treatment visit 30 days (±3 days) after Post-Treatment Visit.

Any adverse event occurred during the study treatment should be monitored by subsequent follow-up visits until resolves to grade 1 or less, or until a new therapy is started.

Subjects who discontinue treatment for any reason, will be followed for survival. In addition off study evaluations will be done when treatment is discontinued -Section 7.0.

15.0 REGULATORY CONSIDERATIONS:

15.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

15.2 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. The participating sites should not make any changes or revision to the protocol.
Any changes or revisions to the protocol must be provided to Dr. Cheng, Montefiore Medical Center and Astellas. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Astellas. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

16.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION:

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

The Montefiore Medical Center, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principle Investigator (Haiying Cheng, MD.) will monitor this study. The case report forms will be monitored every 3 months against submitted support documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. **Astellas will notify the Principle Investigator if an application is filed.**

17. 0 DATA SAFETY AND MONITORING BOARDS:

All trials initiated by the Montefiore Medical Center are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets once a month with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB reviews trial performance information such as accrual information.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).

Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

18.0 STATISTICAL CONSIDERATIONS:

18.1 Study Design/Analytic Plan

- The primary statistical objectives of this single arm open label phase II study to obtain preliminary estimates of the rate of mediastinal nodal clearance and the rate of complete pathologicl response in patients with stage III NSCLC with EGFR mutations who received neoadjuvant erlotinib and had surgical resection. Historical data from the neoadjuvant studies with chemotherapy or chemoradiotherapy in resectable NSCLC patients had mediastinal nodal clearance between 15-40%. We hypothesize that patients with stage III EGFR mutated NSCLC treated with neoadjuvant erlotinib therapy must have comparable rates of mediastinal down staging and complete path response for this strategy to evaluate further in this subset of NSCLC patients.

- The mediastinal nodal clearance is defined as pathologicaly negative N2 disease in the final surgical resection specimen or mediastinoscopy. This can be objectively measured and has been confirmed as the best predictor of long term survival in patients with stage III NSCLC treated with neoadjuvant therapy and had surgical resection.

- Secondary objectives are to estimate objective overall response rate [ORR, i.e., complete response (CR) + partial response (PR)], disease control rate (CR+PR+SD), the surgical resection rate, the progression free (PFS) and overall survival (OS), and the safety of neoadjuvant erlotinib followed by surgical resection in patients with stage III EGFR mutated NSCLC.

- PFS is defined as the time from randomization until documented tumor progression or death from any cause. PFS is censored at the date of the last follow-up visit for patients who are still alive and who have not progressed. OS is defined as the time from the date of randomization to date of death due to any cause.

- Response rates will be summarized by computing proportions and corresponding 95% confidence intervals. Time to event endpoints will be analyzed using standard survival analytic methods, including the Kaplan-Meier approach for estimating the survival distributions. Median time to event and 95% confidence intervals will be estimated from the Kaplan-Meier curves. All primary and secondary analyses will be based on the intent-to-treat principle.

18.2 Sample Size/Accrual Rate

- Our study patient population comprise of the patients with stage III NSCLC who have activating EGFR mutation.

- Based on historical data, the mediastinal nodal clearance rate of 30% or higher will justify the further study of neoadjuvant erlotinib and the rate of 15% or less will be considered ineffective.

- An optimal two-stage phase II study[40] is designed to test the null hypothesis that the rate is 15% or less versus the alternative hypothesis that the response rate is at least 30%.

- The total sample size if the study will be 55 patients

- Nineteen (19) patients will be accrued in the first stage of phase II. **If 3 or fewer responses are observed during the first stage then the treatment will be concluded early for lack of efficacy.** Otherwise, 36 additional patients will be accrued for the second stage. **If 12 or fewer responses among 55 patients are observed by the end of this phase II study, no further investigation of this treatment regimen is warranted.**

- The power under this design is 80% and the type I error is 0.05. The probability of early stopping at the first stage is 68.4% if the true response rate is 15%. If the true response rate is 30%, the probability of early stopping at the first stage is 13.3%.

- By the end of this study, response rate will be estimated and its exact 95% confidence interval will be calculated. A total of 55 patients ensure that the 95% confidence interval for the estimated response rate will be within +/- 15.7%.

- The Montefiore Medical Center will initiate the study. Additional 4-5 sites will be subcontracted by Montefiore Medical Center to expedite accrual in the study.

- With the initial anticipated accrual of 1-2 patients per month across 4-5 centers, it will take approximately 12 months for the first stage of the study. The total e accrual period is assumed to be approximately 24-36 months, with a follow-up period of an additional 12 months after the last patient is enrolled.

18.3 Randomization and Stratification

This will be a single arm phase II study and no randomization or stratifications will be involved

18.4 Evaluation of toxicity.

All patients will be evaluated for toxicity from the time of their first treatment with erlotinib. All of the surgical procedures in the protocol are the usual standard of care in treating patients with stage III NSCLC. However, we will monitor and record all postoperative complications. Certain postoperative complications are expected after lung resection and/or mediastinoscopy. We will particularly monitor 30 day mortality, development of bronchopulmonary fistula or prolong wound healing. If the rate of these is more than what is expected as standard of care, the regulatory authorities will be reported and the trial will be suspended for toxicity.

18.5 Evaluation of response.

All patients who meet the eligibility criteria and have received at least one dose of treatment will be assessed for response to treatment.

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APPENDIX A
MODEL INFORMED CONSENT

Montefiore Medical Center
Albert Einstein College of Medicine of Yeshiva University

Individual's Informed Consent to Participate as a Subject in Clinical Research

TITLE OF STUDY
EValuation of Erlotinib as a Neoadjuvant Therapy in stage III NSCLC patients with EGFR mutations (EVENT trial)

PRINCIPAL INVESTIGATOR:	Haiying Cheng, MD	TELEPHONE NO.: 718-405-8404
OFFICIAL ADDRESS:	1695 EASTCHESTER ROAD Bronx, NY 10461	IRB PROTOCOL NO.:

INTRODUCTION

By signing this form you have voluntarily agreed to participate as a subject in the research study referenced above.

You are being asked to take part in this research study because you have a type of lung cancer called Non-Small Cell Lung Cancer (NSCLC). Your physicians have determined that you have stage III disease and your tumor tested positive for a mutation in a gene called epidermal growth factor receptor (EGFR). The treatment for stage III lung cancer is complex and the standard treatment includes a combination of chemotherapy and radiation followed by surgery. This study will examine the effectiveness of an oral targeted therapy called erlotinib followed by surgery for your particular type of lung cancer. You are being offered this study because your physician thinks that your body is in good condition to receive this treatment followed by surgery to control your cancer.

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision and discuss it with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to develop more effective treatments for patients with stage III lung cancer like you by using effective novel targeted therapy prior to surgery. You are being asked to participate because your tumor has spread to the lymph nodes and hence determined to have stage III disease. The standard treatment options for your

condition will usually includes a combination of chemotherapy and radiation either alone or followed by surgical resection, chemotherapy followed by surgery or in rare cases surgery followed by chemotherapy and radiation.

Recent advances in molecular medicine has enable the physicians to identify the changes in the cancer causing genes called oncogenes in the tumor and develop medicine against these targets. About 15-20% of patients with the type of lung cancer that you have a mutation in a gene called epidermal growth factor receptor (EGFR). Erlotinib (Tarceva®) is an oral medication that targets EGFR. Erlotinib is available as a once a day oral pill. Erlotinib has proven clinical benefit in patients with advanced lung cancer when it is used alone as a single agent. The U.S. Food and Drug Administration (FDA) approved them for commercial use for patients with NSCLC who have failed one prior regimen of chemotherapy in 2004, as a maintenance therapy after chemotherapy in 2010 and recently approved as first line therapy in patients with stage IV disease (where the tumor is spread) and have EGFR mutation.

Recent studies have shown that in patients with advanced lung cancer (where the tumor is spread) with EGFR mutation, single agent erlotinib is more effective than standard chemotherapy in reducing the size of the tumor and delaying the growth of tumor. However, if one drug is used alone, the majority of these tumors develop resistance to this drug over a period of 9-12 months. In addition, the role of erlotinib, in patients with stage III disease, like you, has not been studied.

This study will examine the effectiveness of erlotinib giving prior to surgery in stage III patients with EGFR mutation. You are being offered participation in this study because your physicians have determined that you have stage III disease and your tumor tested positive for EGFR mutation. You will receive two months of treatment with daily oral erlotinib and then be evaluated for surgery. If there is significant shrinkage of the tumor, you will be offered surgery to completely remove your tumor.

This will be a single arm study and all the patients in the study will receive the same kind of treatment.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 55 patients with stage III NSCLC with EGFR mutation will take part in this multi-institution study.

WHAT IS INVOLVED IN THE STUDY

Procedures and Tests Prior the Start of the Study

If you give consent to take part in this study by signing this form, you will have certain tests and procedures (called "screening") to determine that you are not at increased risk for side effects and you are eligible to receive treatment with erlotinib (Tarceva®) followed by surgical resection. If your tumor has not been previously tested for EGFR mutation, your physician will have you signed a separate consent form for testing. This testing is NOT covered by the study.

At this "screening" visit the following will be done. **These are part of regular cancer care:**

- Your study doctor will record your medical history, including your smoking habits, medication list, and perform a physical examination.
- Your medication will be reviewed and your doctor might advise you to avoid some medications during your participation in the study.
- About two (2) tablespoons of blood will be drawn from one of your veins to conduct laboratory tests of blood cell counts (numbers of each type of blood cell), chemistries (elements and minerals in your blood), and blood clotting.
- You will have a PET/CT scan and MRI of the brain, if not already done as a part of your standard work up, to determine the extent of your disease and stage.

If you are a woman who could get pregnant, you will be required to have a pregnancy test prior to entering the study and again after you stop taking erlotinib (Tarceva®). Patients, both females and males with reproductive potential (i.e. menopausal for less than one year and not surgically sterilized) must practice contraceptive measures throughout the study,

Your researcher will review with you all medications that you are taking as some may interact with your therapy and may need to be discontinued.

It is possible that after these tests are reviewed, you will not be able to take part in the study. There may also be other reasons why you cannot participate which will be discussed with you by your doctor.

Treatment

If the screening tests show that you are eligible to participate in the study, you will be asked to return to the clinic once every two week during the treatment with erlotinib. You will be taking erlotinib treatment for about two months then be evaluated for surgery. It is important to understand that taking part in this study requires a commitment from you to visit the clinic for the regular appointments.

Procedures and Tests during the Study

The following examinations and tests will be performed at the clinic during study treatment. **These are part of regular cancer care**:

:

- Your doctor will examine you in the clinic every two weeks while you are on treatment with erlotinib.
- About two (2) tablespoons of blood will be drawn from one of your veins to conduct laboratory tests of blood cell counts (numbers of each type of blood cell), chemistries (elements and minerals in your blood), and blood clotting on the first day of each treatment cycle and once every week during the first treatment cycle.
- If you are taking anticoagulation medicine such as coumadin (warfarin), you will need more frequent blood tests to check blood clotting (PT/INR) as determined by the study doctor (e.g. weekly for first month and weekly for a minimum of 2 weeks following discontinuation of Tarceva® (Erlotinib).
- After 2 months of erlotinib treatment, you will have a PET/CT scan to determine whether you are responding to the treatment (i.e. whether or not the tumor shrunk or remains stable) or not. You will then be evaluated by a surgeon for surgical removal of the remaining tumor. You will continue to take erlotinib until 1day prior to the surgery.
- Your treatment after the surgery will be determined by your treating physician and it will be influenced by your response to treatment with erlotinib.

LABORATORY RESEARCH STUDIES

If you participate in this study, your tumor tissue collected from a previous biopsy or surgery will be sent to researchers to determine several molecular and cellular biomarkers in the tumor. Researchers hope this research will help them understand how your disease responds to the treatment. At the end of this consent, you will also be asked if your blood and a skin biopsy may be collected and used for other laboratory research studies. These additional research studies are optional. Even if you decline the additional research studies below, your tumor tissue will still be sent
for the molecular and cellular tests.

The results of the laboratory research studies will not be sent to you or your doctor, will not be placed in your medical records, and will not affect your care. These tests are for research purposes only.

Drug Treatment

The treatment will be administered in the outpatient clinic. You will not need to be hospitalized to participate in this study unless you experience a serious side effect.

You will take erlotinib (Tarceva®) at a dose of 150 mg daily for approximately two months. After 2 months of erlotinib treatment, you will have a PET/CT scan to determine whether you are responding to the treatment (i.e. whether or not the tumor shrunk or

remains stable) or not. You will then be evaluated by a surgeon for surgical removal of the remaining tumor. You will continue to take erlotinib until 1day prior to the surgery. Your treatment after the surgery will be determined by your treating physician and it will be influenced by your response to treatment with erlotinib.

Tarceva® (Erlotinib)

Tarceva® (Erlotinib) 150 mg in tablet form is to be taken by mouth once daily. Your doctor may reduce the dose of Tarceva® (Erlotinib) if he or she is concerned that you have any significant side effects. The tablet should be taken in the morning with a glass of water. It should be taken at least one hour before or two hours after a meal. Patients should avoid grapefruit juice while on Tarceva® (Erlotinib). If you forget to take your daily dose of Tarceva® (Erlotinib) in the morning you can take the dose later during the day. If you forget to take the tablet one day, you must NOT take the missed tablet the next day.

You will be provided with Tarceva® (Erlotinib) free of charge for the entire time that you are on the study. You will be asked to complete a pill diary for Tarceva® (Erlotinib). We will provide you with the diary. Every dose of medication must be recorded on this diary in order to assure that you are taking the drug properly. You should bring this diary with you on each visit for collection by the research staff.

If you experience serious side effects on either treatment, your doctor may consider reducing your dose or stopping treatment.

Genetic Research

The tests conducted under this research study may reveal genetic information in your tumors. Since the significance of these tests is not known for you and it is not likely to affect your family members, we will not disclose the results of the genetic testing. No formal genetic counseling will be provided under this research study.

GENETIC COUNSELING INFORMATION: You may wish to obtain professional genetic counseling prior to signing the informed consent. A genetic counselor is a person qualified to provide information about what the results of this type of test may mean to you and your family. You or your insurance company will be responsible for the cost of these services.

Please also see the "Study Plan Schema" at the end of this document that outlines this study for you.

HOW LONG WILL I BE IN THE STUDY?

You will receive erlotinib treatment for about two months followed by surgery. You will then be followed on regular basis for about 5 years.

Your treatment in this study will continue as long as six conditions are met:

- You continue to agree to take part in the study and follow the instructions.

- Your disease does not become worse.
- If your medical condition changes during treatment and continuing in the study do not appear to be in your best interest, you will be told, the treatment will be stopped, and other options for your medical care will be discussed with you.
- No severe or life-threatening side effects develop. The drug will be stopped if such side effects develop and appropriate medical care will be provided.
- Your study doctor, the Sponsor, and the Supporters agree to continue to conduct the study and to continue your participation in the study. There may be safety issues or regulatory requirements that would cause the end of your participation in the study or that would end the study altogether.
- For women, you do not become pregnant.

You may stop participating at any time. However if you decide to stop participating in this research study we encourage you to talk to the study doctor first.

POST-SURGICAL FOLLOW-UP

After your surgery, you will be seen in the clinic for post-surgical follow up. At this visit, the following procedures will be performed:

- A physical examination and your vital signs will be recorded.
- Your study doctor will also ask you about any medications you are taking, and about any side effects or symptoms you are having.
- Blood samples (about 2 tablespoons) will be drawn for blood counts, chemistries, and clotting tests.
- X-rays and/or other imaging scans to evaluate your disease may be repeated.
- If you are a woman of childbearing potential, a pregnancy test may be performed if your study doctor believes it is necessary.

After this visit, your study doctor will follow your disease status as needed.

WHAT ARE THE RISKS OF THIS RESEARCH STUDY

Based on the side effects seen in other lung cancer patients after receiving erlotinib (Tarceva®), we can predict some, but not all of the side effects you may have. You may experience some, all, or none of the side effects. You should discuss these side effects with your doctor. You will be watched closely for side effects, and the drug will be stopped if serious side effects develop. Other drugs will be given to make some of the side effects less serious and less uncomfortable. Many side effects go away shortly after the treatment is stopped, but in some cases, side effects can be serious, long lasting, permanent, or life threatening. Death is a rare but possible complication of this treatment.

Tarceva® (Erlotinib) Risks and Discomforts

Tarceva® (Erlotinib) may affect several organs or parts of your body in addition to the potential side effects it may have on cancer cells.

The most common side effects of Tarceva® are rash and diarrhea. These can be controlled with medication or if they become too severe, the Tarceva® treatment may have to be interrupted or the dose reduced. If you have a rash that is bothersome, you should seek advice from your study doctor. In some cases, diarrhea accompanied by nausea, loss of appetite or vomiting may lead to dehydration (loss of too much body fluid) which could cause decreased kidney function. If you have diarrhea that is severe or lasts more than 3 days you should seek advice from your study doctor.

The side effects of Tarceva® may include but are not limited to:

In more than 20% of patients:

- Skin rash
- Diarrhea (this may be treated with anti-diarrhea drugs)
- Loss of appetite
- Tiredness or fatigue
- New or worse shortness of breath
- Cough
- Nausea
- Vomiting
- Infections
- Weight loss (observed in the erlotinib+gemcitabine treatment for pancreatic cancer)
- Dry skin

In 5%-20% of patients:

- Depression (observed in the erlotinib+gemcitabine treatment for pancreatic cancer)
- Headache
- Inflammation of mucous lining of mouth, mouth sore, or mouth ulcer
- Itching
- Dry, red, irritated eyes
- Back pain
- Chest pain
- Joint pain
- Musculoskeletal pain
- Dehydration (loss of too much body fluid)
- Nail infection
- Fever
- Abdominal or stomach pains
- Wind, heartburn or upset somach

- Neuropathy (nerve damage resulting in numbness or tingling)
- Nosebleeds
- Hair loss or thinning
- Constipation

In less than 5% of patients:

- Changes in liver function tests which may indicate liver damage
- Isolated reports of liver failure, including deaths
- Irritation or damage to the cornea (clear part on the front of the eye) which may lead to changes in vision
- Isolated reports of corneal ulcer or perforation
- Irritation of stomach or bowel which may lead to ulcers (lining breakdown) or bleeding
- ILD (Interstitial lung disease). An irritation of the lungs which rarely may be severe and may result in death
- Decreased kidney function
- Isolated reports of low potassium levels and kidney failure, including deaths
- Changes in the sense of taste
- Severe infections
- Increased risk of bleeding which may be worse in patients who have low platelet count, are taking blood thinners, or are taking certain drugs for pain called NSAIDs such as aspirin or ibuprofen
- Fingernail/toenail changes, and/or irritation of skin around nails
- Possible cracking of skin, especially of fingers and toes
- Isolated reports of increased body hair growth or eyelash/eyebrow changes.
- Increased risk of gastrointestinal perforation, especially in patients with a history of ulcers or diverticulitis or who are taking NSAIDs, corticosteroids, or certain types of chemotherapy called taxanes or types of chemotherapy that target blood vessels
- Isolated reports of conditions causing severe blistering or peeling of the skin, including deaths
- Darkening of the skin color in isolated areas (hyperpigmentation)

There is also a possibility of interaction between Tarceva® and statin, a cholesterol reducing drug, which may increase the risk of statin-related muscle problems which on rare occasions can lead to serious muscle breakdown resulting in kidney damage. Therefore, if you are also taking a statin, you should tell your doctor immediately if you experience unexplained muscle pain, tenderness, weakness or cramps. Your doctor may need to interrupt your treatment.

We do not know all the side effects of the study drug or side effects due to a combination of Tarceva® with other drugs or alcohol. Therefore, you should always discuss the use of

alcohol or any drugs (over-the-counter), prescription, illegal) with your doctor while you are in this study.

Anticoagulants

If you are taking or you have been prescribed a blood thinner (anticoagulants) at any time during the study, it is important that you immediately inform your study doctor. The study drug, Tarceva® (Erlotinib), may increase the risk of bleeding if you are taking blood thinners called coumadin or warfarin. Until further related information is available, your doctor will closely follow up with blood tests to control this situation. If you are visiting any other doctor at another site or office, who prescribes you anticoagulants, it is important that you inform him/her about your participation in this study.

Other Potential Risks Include:

Risks Associated with Blood Tests

Side effects associated with blood tests may include infection, bruising, redness, discomfort or bleeding at the injection site.

There may be additional side effects or risks that are not yet known. Please tell your study doctor if you have any new or worsening health problems. Your study doctor will watch you closely during this study.

Women who are pregnant or breast feeding cannot take part in this study because we do not know what effect the treatment will have on an unborn child or if the study drug can be passed to an infant through the mother's milk. If you are a woman capable of having children, you will be given a pregnancy test before you begin the study. If there is a chance you could become pregnant during this study, you should not participate in the study or you must use a highly effective means of birth control [birth control pills, intrauterine device (IUD), or barrier device such as a condom] while you are taking part. If you become pregnant while you are taking part in this study, you must notify one of the doctors listed on this form immediately so that management of the pregnancy and the possibility of stopping treatment can be discussed.

Any male patient whose partner is capable of having children should also use an effective means of birth control (condoms, abstinence) while taking part in this study, because we do not know what effect the treatment may have on the sperm and what effect this would have upon the development of an unborn child.

Risks Associated with surgical procedures

As a part of your treatment for your stage III lung cancer, you will be required to have certain surgical procedures done either as part of your treatment or to determine whether or not you have a good response to treatment. All the surgical procedures in the protocol are the usual standard of care in treating patients with your type and stage of lung cancer. There are potential side effects and risks associated with these procedures. Your surgeon

will discuss with you all the risks and benefits associated with those procedures prior to the surgery. It is your right to accept or decline a procedure that is offered to you. The effect of taking erlotinib, prior to a surgical procedure, is not completely understood. However, the prior studies with erlotinib prior to surgery in lung cancer showed no increase in surgical complications.

ARE THERE ANY BENEFITS TO TAKING PART IN THIS RESEARCH STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Although it is not possible to predict or guarantee whether any personal benefit will result from your participation in this study, one possible benefit is decreasing the size of your tumor by erlotinib followed by complete surgical resection. Although this does not guarantee cure, it may likely increase your chances of being cured or live longer. We also hope the information learned from this study will benefit other patients with NSCLC cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

Your study doctor is very willing to discuss the benefits and side effects of alternative treatments. Instead of being in this study, you have these options: You may receive chemotherapy and radiation alone, chemotherapy and radiation followed by surgery, chemotherapy followed by surgery or surgical resection followed by either chemotherapy alone or chemotherapy and radiation. Other investigational protocols with chemotherapy and radiation may be available for your disease. You may receive no further cancer therapy and best supportive care measures to relieve your symptoms only. Please ask any questions you may have and take as much time as you need to make your decision.

New Information

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your study doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to remove you from the study. He/she will explain the reasons and arrange for your care to continue.

CONFIDENTIALITY (WHO MAY SEE YOUR RECORDS?)

The records of this study will be kept confidential and you will not be identified in any written or verbal reports. Your research records will be kept in a secured area and locked in a file cabinet at Albert Einstein Cancer Center, Montefiore Medical Center. Only those directly involved with the conduct of the study will have access to your medical records. Representatives from Astella Pharmaceuticals, Inc. (Astella, the maker of Tarceva®) or their agents Independent Ethics Committees (IECs), the U.S. Food and Drug Administration (FDA), and certain Drug Regulatory Authorities may review information from the study that contains your identity. Any such review will be held strictly confidential, so as to protect your privacy. **You will also be asked to sign a document called an Authorization to use and disclose your Protected Health Information. This document allows you to give your permission for your health information to be collected, used, and disclosed as necessary to conduct the research study.**

Your research study records may also be inspected by the Montefiore Medical Center Institutional Review Board (IRB), the Albert Einstein College of Medicine Committee on Clinical Investigations (CCI).

COST OF PARTICIPATING

There is no cost to you for erlotinib (Tarceva®). However, you or your insurance company will be paying for the costs of other necessary medications for your disease, routine blood tests, x-rays, scans, other laboratory tests, surgical procedures and your routine medical care. You will not be charged for any research related studies like the laboratory and future research done on your blood tumor or skin biopsy, if you agree.

Insurance companies and Medicare may not pay for costs associated with some requested studies. If your insurance company does not cover the cost of routine care, then you will have to pay these costs. You have the right to ask what it will cost you to take part in this study or to have other treatments. You will not be paid for your participation in this study. One or more of the research personnel is receiving fees for giving presentations on this drug.

INFORMATION ABOUT RESEARCH RELATED INJURY

If you are injured as a result of the research procedures during the course of the study, you should immediately contact your study doctor. If you are injured as a result of this research, only immediate, essential, short-term medical treatment, as determined by the participating hospital or sponsoring company, will be available for the injury without charge to you personally. No monetary compensation will be offered.

WILL ANY OF THE SAMPLES (TISSUE, BLOOD) TAKEN FROM ME BE USED FOR RESEARCH STUDIES?

OPTIONAL BLOOD RESEARCH STUDIES

This study includes one or more laboratory tests that will analyze a small amount of your blood. If you agree to participate in this laboratory research study, 1-2 teaspoons of blood will be collected before you begin treatment and after you have been on Tarceva® (Erlotinib) for at least two weeks. The samples will be collected at the same time blood is being collected for tests used to monitor your health. An additional stick will not be necessary to collect these specimens.

The specimens will be sent to a laboratory, where researchers will study lung cancer cells which may be in the blood. Researchers will perform these tests in order to understand your disease, the response your disease may have to the treatment, and the effect the treatment may have on patients. You may participate in the therapy portion of this research study without participating in the additional laboratory (blood) portion.

Please review the points listed in the "Voluntary Participation and Withdrawal" section, then read the question below and circle "Yes" or "No".

I agree to participate in the blood laboratory research studies that are being done as part of this clinical trial.

Yes _____Initial No _____Initial

OPTIONAL SKIN BIOPSY

A skin biopsy is also being requested of you to determine the patients who will have better response to treatment.

A biopsy is a surgical procedure in which an area is numbed with local anesthetic, and a small sample of skin in the upper back trunk is withdrawn. When the local anesthesia is given, you may initially feel a burning sensation for several seconds. During the actual procedure itself, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your physician for additional local anesthesia or a medication to ease your stress. You also may experience bleeding, and/or bruising after the procedure is completed and you may experience soreness in the area for a few days afterwards. Rarely an infection can develop. A skin biopsy will be done before you begin your treatment and after you have been on Tarceva® (Erlotinib) for at least two weeks. You may participate in the therapy portion of this research study without participating in the biopsy portion.

Please review the points listed in the "Voluntary Participation and Withdrawal" section, then read the question below and circle "Yes" or "No".

I agree to participate in the skin biopsy research studies that are being done as part

of this clinical trial.

Yes _____Initial No _____Initial

FUTURE RESEARCH

USE OF DE-IDENTIFIED SPECIMENS FOR FUTURE RESEARCH

In addition to the research you are consenting to under this research study, Dr Haiying Cheng or other researchers at this or other institutions may wish to study the samples in future research, including genetic analysis. These samples, taken from your body, would NOT be linked back to you. No one will know your name or protected health information.

At this time, the researcher does not know what the future studies will be. Your specimens may also be submitted to a tissue/cell/DNA bank. The specimens may be kept for a long time and may exceed 50 years.

In some research using human blood or tissue, the specimens and their parts may enable researchers to develop medical tests or treatments that have commercial value. You will not receive any money that may result from any such commercial tests or treatments.

Your specimens may be used for future research, even though the purpose of the future research is not known at this time.

PARTICIPANT: PLEASE INDICATE YOUR CHOICE BY INITIALING ONE (1) OF THE FOLLOWING OPTIONS

___ I consent to have my specimens used for future research studies.

___ I consent to have my specimens used for future research studies only for the study of _____.

___ I do NOT consent to have my specimens used for future research studies. The specimens will be destroyed at the end of the study.

WHO TO CONTACT

In the event of a research-related injury or if any questions arise related to this research project, you may call the supervisor of this study Dr. Haiying Cheng at (718) 405-8404.

If you have any questions about your rights as a research subject, you may also call Montefiore Medical Center Institutional Review Board (IRB) at (718) 798-0406, Monday through Friday between 9am and 5pm. or the Albert Einstein Committee on Clinical Investigations (CCI) at (718) 430-2253.

WHERE CAN I GET MORE INFORMATION?

• You may call the National Cancer Institute's (NCI's) Cancer Information Service.
Voice: 1-800-4-CANCER (1-800-422-6237)
TTY: 1-800-332-8615
• Visit the NCI's Web site: http://www.cancer.gov or CancerNet: http://cancernet.nci.nih.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will get a copy of this form. If you want more information about this study, ask your study doctor.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

It is entirely up to you to decide whether or not to take part in this study. If you do decide to take part you will be required to sign this consent form. You are free to choose not to participate in this study or to withdraw from this study at any time and without giving reason. If you choose not to be in the study, wish to withdraw, or if you are asked to leave the study there will be no penalties. In other words, you will not be denied any treatments you may need and it will not affect the standard of care you receive.

You will be asked to complete the procedures described in the section titled "End of Treatment/Follow-up".

IF YOUR STUDY DOCTOR OR SPONSOR(S) CHANGE THEIR MINDS

Your study doctor or the company sponsor(s) may stop your treatment at any time, without your consent if it is determined that you need other treatment, if you have a study-related illness or injury or for any other reason.

You will get a copy of this form.

SUMMARY

You have asked all the questions you want to ask, after reading and listening to an explanation of the following information. If you do not understand English, or if you are unable to read English, this information has been explained to you orally. You have been given a copy of this form whether or not you have agreed to participate in this study.

SIGNATURES

_____

Name of Participant Date

_____

Signature of Participant Date

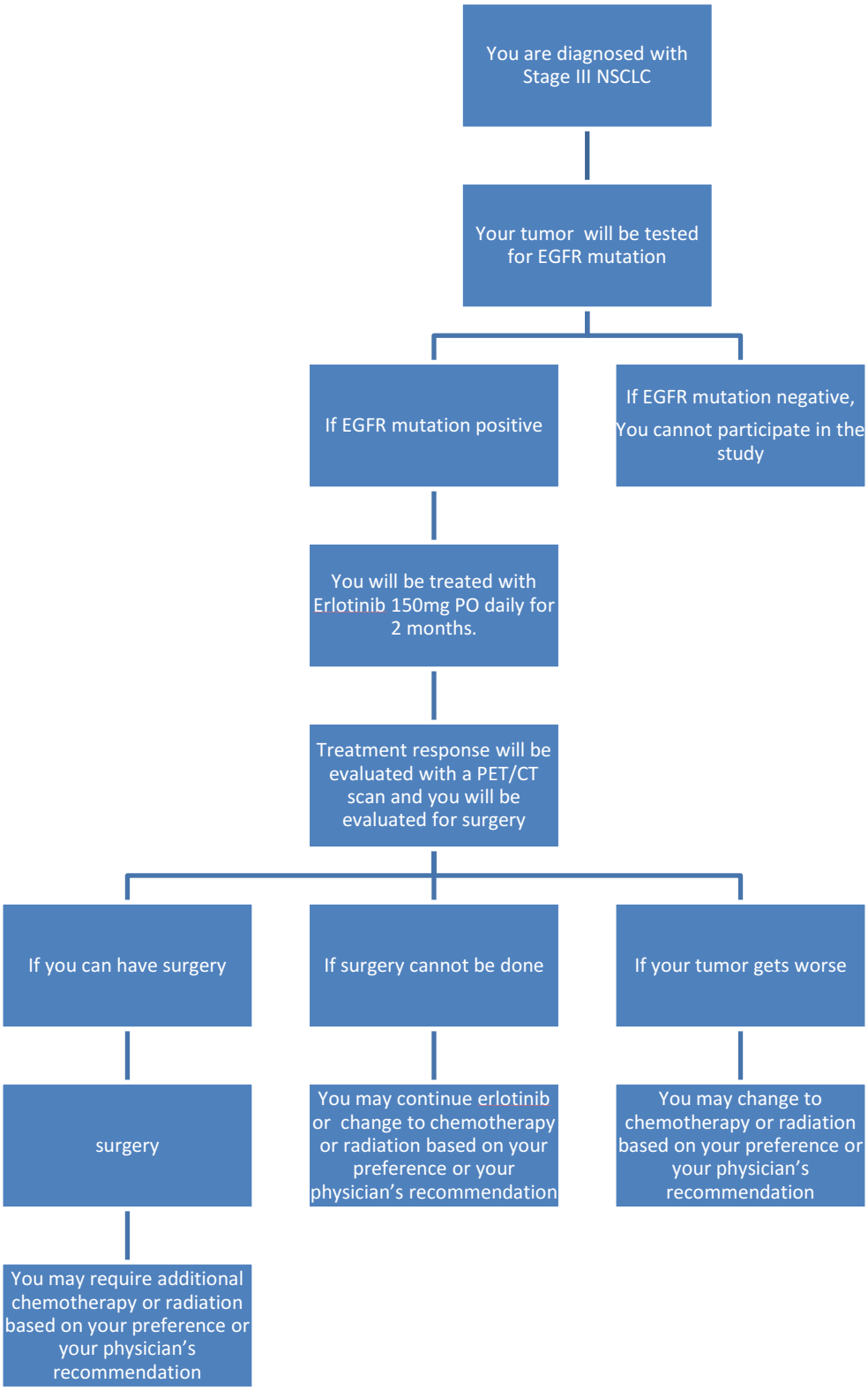
_____

Name of Person Conducting the Informed Consent Process Date

_____

Signature of Person Conducting the Informed Consent Process Date

STUDY SCHEMA



APPENDIX B
ELIGIBILITY CHECKLIST FOR PATIENT REGISTRATION

EValuation of Erlotinib as a Neoadjuvant Therapy in stage III NSCLC patients with EGFR mutations (EVENT trial)

Eligibility Criteria: The answers to the following questions must be '**yes**' in order for the patient to be eligible. N/A should only be answered if description within question allows.	**YES**	**NO**	**N/A**
INCLUSION CRITERIA			
Pathologically proven (either histologic or cytologic) diagnosis of Stage IIIA or IIIB non-small cell lung cancer [according to AJCC Staging, 7th edition; see Appendix E] within 4 weeks of registration. **State Method of Dx: _____ State Date Dx: _____** **State Stage and TNM: _____ Stage _____ T ___ N _____ M0**			
Activating mutation in EGFR oncogene: **check appropriate:** **exon 19 deletion ____** **exon 21 mutation ___** **others ____ (specify_____)**			
No prior chemotherapy or radiation for lung cancer			
Patients may be potentially resectable or unresectable: **check appropriate:** **resectable _____** **unresectable _____**			
Mediastinoscopies or EUS/EBUS to evaluate N3 disease. (Please complete the below) Mediastinoscopy: Yes: ____ No: _____ Date (if yes) _____ Endoscopic ultrasound (EUS) : Yes: ____ No: ___ Date (if yes) _____ Endobronchial ultrasound (EBUS) : Yes: ____ No: ___ Date (if yes) _____ Pathological confirmation of N3 nodes: Yes ____ date: _____ No _____			
Stage III A or B disease, including no distant metastases- based on following diagnostic workup:			

Eligibility Criteria: The answers to the following questions must be '**yes**' in order for the patient to be eligible. N/A should only be answered if description within question allows.	**YES**	**NO**	**N/A**
INCLUSION CRITERIA			
History/physical examination prior to registration. **Date: _____**			
CT Scan of the chest or PET/CT Scan within 28 days of study entry **Date: _____ State Method: _____**			
CT Scan or MRI of abdomen or PET Scan within 28 days of study entry **Date: _____ State Method: _____**			
An MRI of the brain or Head CT Scan with contrast within 28 days of study entry **Date: _____ State Method: _____**			
PFT's:. Must be done within 8 weeks of study entry. **Date: _____**			
EKG: Must be done within 6 weeks of study entry. **Date: _____**			
Patient must have measurable or evaluable disease.			
ECOG performance status 0-2, **ECOG PS (0-2): Numerical Value ____**			
State age in years____ **Date of Birth _____**			
The following minimum required laboratory data must be done within 14 days of treatment.			
Absolute neutrophil count ≥1,500 cells/ul: **Numerical value _____ Date of test _____**			
Platelets ≥ 100,000 cells/ul **Numerical value _____ Date of test _____**			
Hemoglobin ≥ 9.0 g/dl **Numerical value_____ Date of test _____**			
Serum creatinine ≤ 1.5 x ULN **Numerical value_____** **Institution ULN _____ Date of test _____**			

Eligibility Criteria: The answers to the following questions must be '**yes**' in order for the patient to be eligible. N/A should only be answered if description within question allows. **INCLUSION CRITERIA**	**YES**	**NO**	**N/A**
Total Bilirubin < 2.0 x institutional upper limits of normal **Numerical value_____** **Institution ULN _____ Date of test _____**			
AST and ALT ≤ 2.5 x the ULN **Numerical value_____** **Institution ULN _____ Date of test _____**			
For women of Child-bearing potential: **A negative serum or urine pregnancy test (sensitivity ≤ 25IU HCG/L) within 72 hours prior to the start of study drug administration** **Beta HCG: State results: _____** **Date of test_____** **State date of Rx_____**			
Persons of reproductive potential must agree to use and utilize an adequate method of contraception throughout treatment and for at least 4 weeks after study drug is stopped. Prior to study enrollment, men and women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. **Does patient agree to use adequate method of contraception?**			
Ability to take oral medication			
Patient signed the study specific informed consent. *(The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.)* **Date signed: _____** **Version: _____** **Expiration date of ICF: _____**			

The support documentation, per the requirements under the study parameters section of each the protocol, as well as the consent form and this checklist, must be faxed to the Montefiore Medical Center, Central Protocol Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

a. Signed Consent Form Enclosed _____ Not Enclosed _____Not Applicable ____
b. Eligibility Form Enclosed _____Not Enclosed _____ Not Applicable _____
c. Pathology Report(s) Enclosed _____Not Enclosed _____ Not Applicable _____
d. EGFR mutation Results Enclosed _____Not Enclosed _____ Not Applicable _____
e. Lab Report(s) Enclosed _____Not Enclosed _____ Not Applicable _____
f. Cat Scan/MRI Report(s)Enclosed _____Not Enclosed _____ Not Applicable _____
g. PET/CT Report(s) Enclosed _____Not Enclosed _____ Not Applicable _____
h. PFT Enclosed _____Not Enclosed _____ Not Applicable _____
i. EKG Enclosed _____Not Enclosed _____ Not Applicable _____
j. Surgical Evaluation Enclosed _____Not Enclosed _____ Not Applicable _____
k. Mediastinoscopy report Enclosed _____Not Enclosed _____ Not Applicable _____
l. EUS/EBUS report Enclosed _____Not Enclosed _____ Not Applicable _____
m. Specimens (as applicable): Date Sent __Type of Specimen _____ Sent To_____
n. Other _____ Enclosed _____Not Enclosed _____

IRB approval date of protocol: _____ Hospital where patient will be treated: _____

Date patient will begin treatment: _____ Primary Physician: _____

The patient (full name) _____ has met the above protocol criteria on _____

and is assigned the sequence number _____

Your signature: _____

Please e-mail this form along with registration worksheet provided by Montefiore to cpdmu-registration@montefiore.org. Please copy the regulatory and study coordinator at Montefiore Medical Center, along with the Principal Investigator at Montefiore.

APPENDIX C

NCI CTCAE Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from **http://ctep.info.nih.gov**. All appropriate treatment areas have access to a copy of the CTC Version 4.0

APPENDIX D

ECOG PATIENT PERFORMANCE STATUS

STATUS	SCALES KARNOFSKY	**ZUBROD-ECOG-WHO**	**STATUS**
No complaints	100	**0**	**Normal activity**
Able to carry on normal activities	90	**1**	**Symptoms, but fully ambulatory**
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	**2**	**Symptomatic, but in bed <50% of the day**
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	**3**	**Needs to be in bed >50% of the day, but not bedridden**
Disabled, requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death non imminent	30	**4**	**Unable to get out of bed**
Very sick. Hospitalization Necessary. Active support treatment necessary	20		
Moribund	10		
Dead	0		

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536.

APPENDIX E

Case Report Forms

Please see attached CRF.

APPENDIX F AJCC TNM staging system for lung cancer (7th edition, 2007)

TNM staging system for lung cancer (7th edition)

Primary tumor (T)			
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus		
T1a	Tumor ≤2 cm in diameter		
T1b	Tumor >2 cm but ≤3 cm in diameter		
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features:		
	Involves main bronchus, ≥2 cm distal to carina		
	Invades 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		
T2b	Tumor >5 cm but ≤7 cm		
T3	Tumor >7 cm or any of the following:		
	Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)		
	Atelectasis or obstructive pneumonitis of the entire lung		
	Separate tumor nodules in the same lobe		
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe		
Regional lymph nodes (N)			
N0	No regional lymph node metastases		
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension		
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion		
M1b	Distant metastasis (in extrathoracic organs)		
Stage groupings			
Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,T1b,T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,T1b,T2a,T2b	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 or M1b

Adapted from: Goldstraw, P, Crowley, J, Chansky, K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groups in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007; 2:706.