Phase II Study of Bevacizumab and Erlotinib in Elderly Patients with Advanced Non-Small Cell Lung Cancer

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Schema:

Bevacizumab 15 mg/kg IV Q 3wks

Erlotinib: 150 mg PO daily

Cycle length: 21 days

Treatment continued until disease progression or intolerable toxicity

1.0 Background

1.1 Disease Background

Lung cancer is the number one cause of death from cancer in both men and women. In particular the elderly (age >65) comprise more than 45% of newly diagnosed advanced NSCLC, but are inadequately represented in the therapeutic literature – rarely more than 20% of the populations studied. Based on the retrospective analysis of two large trials (SWOG 9509, SWOG 9308)[1,2], elderly lung cancer patients tend to have more co-morbidities, increased toxicity to cytotoxic chemotherapy, and trend towards worsened overall survival. It has been reported in the ELVIS trial[3] that the fit elderly (Performance Status 0-1) appear to benefit from systemic therapy (compared to best supportive care) with respect to quality of life (QOL) and overall survival, but many older patients decline systemic chemotherapy because of the perceived increased toxicity. Less toxic and more effective alternatives are obviously needed in elderly patients with advanced non-small cell lung cancer (NSCLC).

In the literature, there is no definite evidence of superiority for one systemic therapy over another. But the introduction of new targeted therapies into clinical practice has lead to an improvement in the survival and overall response rates of patients with advanced lung cancer. This study, first of its kind, explores the response rate of combination treatment with bevacizumab and erlotinib in treatment-naïve elderly patients with advanced NSCLC – an important cohort that need less toxic therapies.

1.2 Vascular Endothelial Growth Factor (VEGF) and Anti-angiogenic Therapy

Folkman and others have provided compelling evidence linking tumor growth and metastases with angiogenesis[4]. Of the identified angiogenic factors, VEGF is the most potent and specific and has been identified as a crucial regulator of both normal and pathologic angiogenesis[5]. VEGF produces a number of biologic effects, including endothelial cell mitogenesis and migration, induction of proteinases, leading to remodeling of the extracellular matrix, increased vascular permeability, and maintenance of survival for newly formed blood vessels[5]. The biologic effects of VEGF are mediated through binding and stimulation of two receptors on the surface of endothelial cells: Flt-1 (fms-like tyrosine kinase) and KDR (kinase domain region)[5,6].

Increased expression of VEGF has been measured in most human tumors examined to date, including tumors of the lung, breast, thyroid, gastrointestinal tract, kidney, bladder, ovary, and cervix, as well as angiosarcomas and glioblastomas[5]. Inhibition of VEGF by using an anti-VEGF monoclonal antibody blocks the growth of a number of human cancer cell lines in nude mice[5]. In addition, the combination of anti-VEGF antibody and chemotherapy in nude mice injected with human cancer xenografts results in an increased antitumor effect compared with antibody or chemotherapy treatment alone[7].

To test the hypothesis that inhibition of VEGF in patients with cancer results in clinical benefit, a recombinant humanized version of a murine anti–human VEGF monoclonal antibody, named Avastin (bevacizumab; previously known as rhuMAb VEGF), was created[8]. Based on results of non-clinical efficacy and toxicology studies, bevacizumab was advanced into clinical

development by Genentech, Inc. for use as a single agent and combined with chemotherapy to induce tumor shrinkage in patients with solid tumors.

1.3 Epidermal Growth Factor Receptor Expression and Significance in Cancer

The control of cell growth is mediated by a complex network of signaling pathways responsive to external influences, such as growth factors, as well as to internal controls and checks. Epidermal growth factor (EGF) was one of the first growth factors to be described. It was shown to be mitogenic, an effect mediated by the binding of EGF to a cell surface EGF receptor (EGFR), stimulating autophosphorylation of the intracellular tyrosine kinase domain of the receptor. Subsequent investigations revealed EGFR to be one of a family of closely related receptors that includes EGFR (HER1), HER2, HER3, and HER4.

EGFR and other HER family members are considered to be important in the development, progression, and aggressive behavior of human epithelial malignancies and to be relevant therapeutic targets. A number of human malignancies are associated with aberrant or over-expression of EGFR[38]. Stimulation of tumor cells via the EGFR is important for both tumor growth and tumor survival in vivo. Over-expression of EGFR in certain human tumors, including NSCLC, has been correlated with both chemo-resistance and poor prognosis[9-15]. Inhibitors of EGFR tyrosine kinase activity (EGFR TKIs) have been in development for a number of years, and although earlier compounds lacked specificity and potency, newer compounds have proven active in non-clinical and clinical studies[16,17].

Tarceva (erlotinib hydrochloride; previously known as OSI-774) is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. Early clinical data with erlotinib indicate that the compound is generally safe and well tolerated at doses that provide the targeted effective concentration based on non-clinical experiments. A recently completed, randomized, double-blind, placebo-controlled trial has shown that erlotinib as a single agent significantly improves the survival of patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease[18].

1.4 Bevacizumab: Background and Clinical Experience

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF). Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two postmarketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

These clinical trials have included patients with a number of tumor types, including colorectal, breast, lung, and renal carcinoma.[19-22].

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition

of bevacizumab, a monoclonal antibody directed against VEGF, to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.0001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.0001$), overall response rate (35% vs. 45%; $p < 0.01$), and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm[19].

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer (CRC).

Additional data from Phase III trials in metastatic CRC (E3200), non–small cell lung cancer (NSCLC; E4599), and metastatic breast cancer (E2100) have also demonstrated clinical benefit from bevacizumab when added to chemotherapy. In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated CRC patients.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; $p = 0.003$). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006. Finally, patients with untreated metastatic breast cancer (E2100) who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively; HR = 0.48; $p < 0.0001$) (see the Bevacizumab Investigator Brochure for additional details).

1.4.1 Bevacizumab in Unresectable, Non-Squamous, Non-Small Cell Lung Cancer

The safety and efficacy of Bevacizumab in patients with non-small cell lung cancer was investigated in a randomized Phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG 4599)[23].

In this multicenter trial, more than 800 patients were randomly assigned to receive chemotherapy with standard doses of carboplatin and paclitaxel (PC) or the same regimen with the addition of bevacizumab every three weeks at a dose of 15 mg/kg IV (PCB) given on day one along with the chemotherapy. Patients were all treatment naïve, with locally advanced, recurrent or metastatic disease. Patients with squamous histology, evidence of brain metastasis, uncontrolled hypertension, on anticoagulation therapy, unstable angina or a history of hemoptysis (more than half a teaspoon) were excluded. After completion of chemotherapy, patients continued to receive bevacizumab alone every three weeks until disease progression or unacceptable toxicity. The primary

endpoint of the study was overall survival and secondary endpoints included response rate, time to progression and tolerability.

Overall survival was statistically significantly better in the PC plus bevacizumab arm. The median overall survival was 12.3 months vs. 10.3 months in the control group (hazard ratio 0.80). Response rate (10% vs. 27%) and time to progression (4.5 mos vs. 6.4 mos) also favored the bevacizumab arm. Toxicities included grade 4/5 neutropenia (16.4% vs. 24%); grade 3/4 thrombosis/embolism (3% vs. 3.8%); & hemorrhage (1.0% vs 4.1%). There were 11 treatment-related deaths (arm PC: 2; arm PCB: 9); 5 due to hemoptysis, all on the bevacizumab arm. Bases on this trial, in October 2006, the FDA granted approval of this regimen for patients with locally advanced or metastatic non-squamous non-small cell lung cancer.

1.5 Clinical Experience with Erlotinib

As of April 2004, erlotinib has been studied clinically in more than 4000 healthy subjects and patients (excluding patients exposed to placebo) in a number of Phase I, II, and III studies.[24]

1.5.1 Dose Selection for Single-Agent Trials of Erlotinib

Phase I trials of erlotinib explored both schedule and dose to evaluate the safety, tolerability, and pharmacokinetic profile of the compound given as a single agent A number of pharmacokinetic trials in healthy subjects have been conducted, along with three classic Phase I trials in patients with advanced cancer. The single-agent maximum tolerated dose (MTD) was estimated to be 150 mg administered once daily.

The primary toxicities of single-agent erlotinib consisted of rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache. When given daily, dose-limiting toxicity (diarrhea) was observed at 200 mg/day. At 150 mg/day, diarrhea was manageable with the addition of loperamide therapy; this dose was considered the maximal tolerated dose.

Rash (variously referred to as dermatitis, acneiform rash, or maculopapular rash) has been variable in onset, duration, and severity, but typically appears on the face, neck, scalp, chest, and back starting after ~1 week of treatment. The mechanistic basis of the rash remains uncertain; histopathologic examination of biopsies of the rash demonstrated inflammatory cell infiltrate and mild epidermal hyperproliferation. In some cases, the rash gradually improved despite continued dosing and, in general, resolved without sequelae following erlotinib discontinuation. The rash did not result in study discontinuation in patients with cancer in the Phase I trials.

Laboratory abnormalities observed infrequently with single-agent erlotinib involved primarily liver function tests, including elevation of ALT, AST, and/or bilirubin.

Selection of the 150 mg/day dose of erlotinib for subsequent single-agent studies was based on pharmacokinetic parameters, as well as the safety and tolerability profile of this

dose in Phase I trials in heavily pretreated patients with advanced cancer. Drug levels seen in patients with cancer receiving the 150 mg/day dose were consistently above the average plasma concentration of 500 ng/mL targeted for clinical efficacy.

1.5.2 Pharmacokinetics

Oral erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at 3 hours after oral dosing of 150 mg/dL at steady state. A study in healthy subjects provided an estimate of bioavailability of 59% (95% CI: 55%, 63%). The time to reach steady-state plasma concentration was ~5 days. The accumulation ratio with daily dosing of erlotinib was estimated to be 2.0. From a population pharmacokinetic analysis of 708 patients, the median trough concentration (C_{min}) 24 hours following the previous dose was 1041 (±697) ng/mL. Median AUC achieved during the dosing interval at steady state was 19,801 ng/hr/mL. Exposure after an oral dose is increased by food.

There is extensive binding of erlotinib and metabolites to both serum albumin and AAG (alpha-1-acid glycoprotein), with total plasma protein binding for erlotinib and OSI-420 of ~95% and 91%, respectively. Erlotinib is extensively metabolized in the liver by the hepatic cytochromes in humans—primarily by CYP3A4 and to a lesser extent by CYP1A2. The primary metabolite of erlotinib, OSI-420, has potency comparable to that of erlotinib, but is present at levels that are < 10% of erlotinib levels. Erlotinib is excreted predominantly via the feces (> 90%). The elimination half-life after a 150-mg oral dose is ~30 hours. In population-based data analyses, no relationships were identified between predicted steady-state trough concentration and patient age, body weight, sex, ethnicity, or creatinine clearance.

1.5.3 Phase II and III Trials in Patients with Advanced Cancer

Multiple Phase II trials evaluating the safety, tolerability, and antitumor activity of erlotinib have been conducted in patients with advanced, refractory malignancies including cancer of the head and neck, lung, aerodigestive tract, ovary, breast, central nervous system (glioma), and others[25-29]. Erlotinib has been evaluated both as a single agent and administered concurrently with conventional chemotherapy agents using various doses and schedules.

Evidence of activity has been observed in squamous cell carcinoma of the head and neck, ovarian, breast and pancreatic carcinoma, non–small cell lung cancer (NSCLC), and glioblastoma multiforme (GBM). Patients received 150 mg/day of erlotinib in all of these studies except the GBM study where dose escalation was allowed until limited by rash and where a higher starting dose was tested in subjects receiving concomitant enzyme inducing anti-epileptic drugs. Dose reduction was allowed in all studies in the case of intolerance. Diarrhea was treated with loperamide therapy and/or dose reduction. Rash was treated with a variety of agents, including oral and topical antibiotics, corticosteroids, and other agents.

Patients receiving erlotinib in combination with various chemotherapy agents have generally experienced the same type of adverse events (AEs) as with either agent alone.

The first randomized placebo controlled trial to demonstrate a survival advantage for an EGFR inhibitor was the Phase III study, BR.21. This international trial, conducted by the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG), included 731 patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease. Patients randomized in a 2:1 ratio to single-agent Erlotinib 150 mg/day obtained a 42.5% improvement in median survival over placebo, from 4.7 to 6.7 months. The one-year survival increased significantly (from 22% to 31%) as did the median and 6 month progression-free survival, response rate, and the time to deterioration of tumor related symptoms of pain, cough, and dyspnea.[18] .

In BR.21, of the 727 patients evaluable for safety (485 erlotinib, 242 placebo), the most common AEs in the erlotinib arm were rash (75% erlotinib, 17% placebo), diarrhea (54% erlotinib, 18% placebo) and stomatitis (17% erlotinib, 18% placebo) events. The majority of these events were mild to moderate in severity. The incidence of interstitial lung disease (ILD) reported was the same in the placebo and erlotinib groups at 0.8% in each arm.

Two large, Phase III, randomized studies in first-line NSCLC patients evaluated erlotinib in combination with platinum-based two-drug combination chemotherapy. A total of 1079 previously untreated patients received carboplatin/paclitaxel with either erlotinib or placebo in the TRIBUTE trial (OSI2298g) conducted in the United States[30]. An additional 1172 patients received cisplatin/gemcitabine plus either erlotinib or placebo in the TALENT trial (BO16411) conducted in 27 countries in Europe and other ex-U.S. locations[31]. Neither study met its primary endpoint of improved overall survival or a secondary endpoint of improved time to disease progression or overall response rate. Overall, the number of adverse events and serious adverse events were well balanced between the two arms of each study, with two exceptions. As expected, rash and diarrhea occurred more frequently in the Erlotinib arms. In the TRIBUTE study, more serious adverse events resulting in death were seen in the Erlotinib arm compared with the placebo arm (53 vs. 27). Most of the apparent imbalance was due to events reported as pneumonia or progression of underlying cancer.[30,31].

1.5.4 Patients with Hepatic or Renal impairment

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

carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs.

A pharmacokinetic (PK) study (data on file) in patients with advanced solid tumors and moderate hepatic impairment according to the Child-Pugh criteria has been completed. In this study, 10 of the 15 patients died on treatment from progressive disease, one patient died from hepatorenal syndrome and one patient died from rapidly progressing liver failure. Six out of the 10 patients who died had baseline total bilirubin > 3 ULN suggesting severe, rather than moderate, hepatic impairment, highlighting the limitations of utilizing the Child-Pugh criteria in an oncology patient population. All patients had hepatic impairment due to advanced cancer with liver involvement such as hepatocellular carcinoma, cholangiocarcinoma, or liver metastases.

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

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

1.6 Bevacizumab and Erlotinib Combination Studies

The strategy for combining therapeutic agents in cancer treatments has been successful in multiple tumor types, including NSCLC. A new series of clinical studies are now being designed and conducted to evaluate the combination of bevacizumab with erlotinib, particularly in NSCLC and renal cell carcinoma[32,33]. This approach has scientific rationale because the two agents target different pathways involved in tumor growth and non-clinical studies in xenograft models have demonstrated that the combination of bevacizumab and erlotinib results in greater efficacy than either agent alone. Furthermore, because there is little to no overlap in toxicity profile between the two agents, the combination is expected to be well tolerated and may provide even greater benefit for patients who are unable to receive cytotoxic therapy.

An investigator-sponsored Phase I/II trial (OSI2486s) has been conducted to evaluate the combination of bevacizumab and erlotinib in subjects with relapsed or refractory NSCLC with non-squamous histology[32]. This Phase I study evaluated three dose combinations to determine tolerability and pharmacokinetic profile of each agent when combined. Subjects whose disease had progressed following at least one chemotherapy regimen for advanced disease (Stage IIIb or IV) were treated with 100 mg/day erlotinib + 7.5 mg/kg Bevacizumab every 3 weeks, 100 mg/day erlotinib + 15 mg/kg bevacizumab every 3 weeks, or 150 mg/day erlotinib + 15 mg/kg bevacizumab every 3 weeks. A total of 12 subjects were enrolled and treated (3, 3, and 6 per cohort, respectively). No dose-limiting toxicities were observed, and the pharmacokinetic profiles of both drugs did not appear to be affected by the combination.

For the Phase II portion of the study, 22 subjects were evaluable for safety and efficacy, inclusive of the 12 subjects treated in Phase I. The majority of the subjects had a good performance status (11 with a Karnofsky score of 90%), adenocarcinoma histology (14 of 22 subjects), and fewer than two prior chemotherapy regimens (16 of 22). The most common

adverse events were rash (20 of 22 subjects), diarrhea (14 of 22), proteinuria (11 of 22), and nausea (9 of 22). All of the events were Grade 1 or 2. There was one episode of Grade 1 hemoptysis and one episode of Grade 3 hypertension. Eleven of the 22 subjects (50%) experienced progressive disease after the first 6 weeks of therapy. Four partial responses (18.8%) and seven instances of stable disease (31.2%) were reported. Based on the preliminary data from this single-arm, Phase I/II study, it appears that the combination of bevacizumab and erlotinib is well tolerated by most subjects at maximum doses and has encouraging activity, supporting a larger, controlled study to assess the efficacy and tolerability of the regimen.

At the recent ASCO meeting, Fehrenbacher presented an abstract from a study were patients with NSCLC were randomized to three different arms: chemo plus placebo, chemo plus bevacizumab and erlotinib plus bevacizumab (AT). In this population (not limited to the elderly), the serious adverse event rates were somewhat less common in the erlotinib plus bevacizumab arm compared to the other two arms. There was one case of a pulmonary hemorrhage in this arm vs. two in the chemo plus bevacizumab arm. Study discontinuation due to adverse events were also less frequent in the AT arm. Efficacy was similar to the chemo plus bevacizumab arm and better that the chemo alone group[34]. Hence the safety of this regimen has been tested and validated in a broader population of patients with advanced NSCLC.

1.7 Study Rationale

The elderly (age $\geq$ 65) comprise more than 40% of newly diagnosed advanced NSCLC, but are inadequately represented in the published therapeutic literature – rarely more than 20% of the populations studied. Based on the retrospective analysis of two large trials (SWOG 9509, SWOG 9308)[1,2], elderly lung cancer patients tend to have more co-morbidities, enhanced toxicity to cytotoxic chemotherapy, and trend towards worsened overall survival. It has been reported in the ELVIS[3] trial that the fit elderly (PS 0-1) appear to benefit from systemic therapy (compared to best supportive care) with respect to QOL and overall survival, but many older patients refuse systemic chemotherapy because of the perceived increase in risk of toxicity. Less toxic alternatives are obviously needed in elderly patients with advanced NSCLC who are chemo-averse or who appear vulnerable or frail, even if their performance status technically is intact.

In the literature, there is no definite evidence of superiority for one systemic therapy over another. Erlotinib is a well-tolerated EGFR-TKI which has been extensively tested in advanced NSCLC patients, especially in heavily pre-treated patients. With the exception of a pilot trial in Boston, single agent erlotinib has not been studied exclusively in the elderly; and the combination of erlotinib and bevacizumab has never been studied exclusively in the treatment-naïve elderly. This study, first of its kind, will explore the response rate in treatment-naïve elderly patients with advanced NSCLC –an important cohort that needs less toxic therapies.

2.0 OBJECTIVES

2.1 Primary

The primary objective of this Phase II study is to evaluate the progression free survival of combination bevacizumab and Tarceva (erlotinib) as first line therapy in elderly patients with

advanced non-small cell lung cancer.

2.2 Secondary

- To evaluate overall survival of combination bevacizumab and Tarceva (erlotinib) as first line therapy in elderly patients with advanced non-small cell lung cancer.
- To evaluate one year survival of patients treated with this combination
- To evaluate the safety of combining bevacizumab with erlotinib in elderly patients with previously untreated advanced NSCLC
- To evaluate the efficacy of combining bevacizumab with erlotinib in elderly patients with previously untreated advanced NSCLC, as measured by objective response rate, duration of response, and disease-related symptom improvement and time to symptom progression [based on quality of life assessments as measured by the seven-item Lung Cancer Subscale (LCS) symptom score of the Functional Assessment of Cancer Therapy-Lung (FACT-L)] (Appendix G)
- To correlate survival with baseline co-morbidities (Charlson Co-Morbidity Index)[35](Appendix H)

3.0 Study Design

This is a phase II open label study for elderly patients with advanced NSCLC that have not received chemotherapy for advanced disease. All patients will be treated with the same regimen.

3.1 Description of the Study

The dose of bevacizumab in this study is 15 mg/kg administered by IV infusion on the first day of each 3-week cycle.

The dose of erlotinib is 150 mg/day orally starting on cycle 1 day 1. Tablets should be taken at the same time each day with ~200 mL (6–8 ounces) of water at least 1 hour before or 2 hours after a meal.

Quality of Life assessments using FACT-L will be collected at baseline and at the end of every second cycle of therapy (e.g. cycle 3 day 1, cycle 5 day 1).The FACT-L can be done after every 3rd cycle after 1st 6 months.

3.2 Rationale for Study Design and Dosing

Standard doses of both drugs are chosen for this trial. There is ample evidence in support of the dosage and scheduling of both of these drugs with adequate clinical experience with regards to potential toxicities and their management. The combination of two, well-tolerated and new targeted therapies with different mechanisms of actions could be potentially more active than either one alone. Obviously the toxicities and potential unwanted interactions are also possible but less likely based on the clinical experience with both drugs. Also, given the patient population chosen for this study, the choice of two easy to administer and relatively safe drugs is

important.

3.3 Outcome Measures

3.3.1 Primary Outcome Measures

The primary efficacy outcome measure for this study is progression free survival, defined as the time from registration to documented disease progression, as determined by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST; Section 12), or death on study, whichever occurs first.

3.3.2 Secondary Outcome Measures

The secondary efficacy outcome measures are as follows:

- Overall survival, defined as the period from the date of enrollment until the date of patient death from any cause.
- One year survival of patients treated with this combination.
- Time to symptom progression, defined as the period from the date of enrollment until the date of symptom progression, as measured by the seven-item Lung Cancer Subscale (LCS) symptom score of the Functional Assessment of Cancer Therapy-Lung (FACT-L)
- Objective response, as determined by the investigator using RECIST
- Duration of objective response, defined as the period from the date of partial or complete response (PR or CR) until the date of disease progression, as determined by the investigator using RECIST
- Symptom improvement rate at baseline and at the end of every second cycle of therapy, or after every third cycle of therapy; after the first 6 months; as measured by the seven-item LCS of the FACT-L (see Appendix G)
- Evaluation of the relationship between molecular exploratory markers and efficacy outcomes

4.0 Study Subjects

Patients are eligible for this first-line therapy study if they have advanced NSCLC. Additional specific inclusion and exclusion criteria are listed below.

4.1 Inclusion Criteria

Patients must fulfill all of the following criteria to be eligible for study entry:

- Female or male aged ≥ 65 years with cytologically or histologically confirmed NSCLC – locally advanced, stage IIIA or stage IIIB (malignant pleural or pericardial effusion or pleural implants) OR stage IV OR recurrence after primary surgery or radiotherapy
- ECOG Performance Status 0-1

- Measurable disease by RECIST criteria (see section 12). Previous irradiated tumor is acceptable as long as there is at least a 20% increase in the size of the previously irradiated lesion
- ANC > 1500/mm³, platelets > 100,000/mm³
- Total bilirubin < = 1.5 mg/dl, SGOT (AST) and SGPT (ALT)≤ 5 x ULN
- Serum creatinine < = 3.0 mg/dl
- Serious, active infections must be controlled. Patients may be enrolled while still on antibiotics as long as clinical signs of active infection are absent.
- Previous radiation allowed provided the patient has recovered from the side effects
- Availability of archival diagnostic tissue (paraffin tissue block, cytospin block from a fine needle aspirate, or unstained slides from resected tumor, core biopsy, or fine needle aspirate) is desirable but not required. IHC and FISH for EGFR expression will be performed. Patient selection is not based on EGFR expression.
- Able and willing to sign an informed consent and HIPAA authorization
- Able and willing to swallow and absorb orally administered medications.
- Women of childbearing potential (WOCBP) and men who are sexually active with WOCBP must agree to use effective methods of contraception during active treatment and for a minimum of 2 weeks after the last dose of study treatment.

4.2 Exclusion Criteria

Patients meeting any of the following criteria will be ineligible for study entry:

- Urine protein: Proteinuria as demonstrated by UPC ratio of ≥ 1.0 based on a spot urinalysis (See Appendix F). Urine dipstick is not permitted at baseline.
- Prior treatment with an investigational or marketed inhibitor of the EGFR pathway or anti-angiogenesis agent (this includes thalidomide)
- Prior treatment for advanced stage disease, with the exception of surgery or radiation (no chemotherapy for advanced disease allowed). Chemotherapy prior to the diagnosis of advanced disease, such as in the adjuvant setting, is allowed.
- History of gross hemoptysis (defined as bright red blood of at least half a teaspoon per episode) within 1 month of enrollment unless definitively treated with surgery or radiation. Hemoptysis post bronchoscopy is not cause for exclusion
- Evidence of significant bleeding diathesis or coagulopathy or other serious or acute internal bleeding (in the absence of therapeutic anticoagulation) within 6 months of enrollment
- Current, ongoing treatment with full-dose warfarin or its equivalent (i.e., unfractionated and/or low molecular weight heparin). May have been off treatment or on treatment at a sub-therapeutic level for any period of time.
- Current or recent (within 10 days of first dose of study treatment) use of aspirin (> 325 mg/day) or other non-steroidal anti-inflammatory drugs (NSAIDs) with anti-platelet activity. Treatment with dipyridamole, ticlopidine, clopidogrel, and/or cilostazol is also not allowed. PRN use of NSAIDs once the protocol treatment has been started is allowed. Low dose ASA (≤ 325 mg/day) is allowable.
- Prior malignancy within the past 3 years other than basal cell carcinoma, cervical in situ.

- History of hemorrhagic or thrombotic stroke, transient ischemic attach (TIA) or other CNS bleeding within the last 6 months. Clinically significant peripheral vascular disease such as active, symptomatic PVD, peripheral arterial thrombosis, aortic aneurysm, requiring surgical repair within 6 months of enrollment.
- Known CNS disease, except for treated brain metastasis. Treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Anticonvulsants (stable doses) are allowed. Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded.
- Uncontrolled or unstable co-morbidities which would clearly preclude use of bevacizumab or erlotinib.
- Lung carcinoma of squamous cell histology (mixed tumors will be categorized by the predominant cell type unless small cell elements are present, in which case the patient is ineligible). Sputum cytology alone is acceptable. Patients with extrathoracic-only squamous cell NSCLC are eligible. Patients with only peripheral lung lesions of any NSCLC histology will also be eligible. A peripheral lesion is defined as a lesion in which the epicenter of the tumor is $\leq$2 cm from the costal or diaphragmatic pleura in a three-dimensional orientation based on each lobe of the lung and is >2 cm from the trachea, main, and lobar bronchi.
- Current, recent (within 4 weeks of enrollment of this study), or planned participation in an experimental drug study other than a Genentech-sponsored bevacizumab cancer study
- Blood pressure of >150/100 mmHg, that cannot be ameliorated with standard anti-hypertensives. Antihypertensives may be started prior to enrollment to reduce BP to acceptable range.
- Prior history of hypertensive crisis or hypertensive encephalopathy.
- Unstable angina
- New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix E)
- History of myocardial infarction within 6 months of enrollment
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to enrollment, anticipation of need for major surgical procedure during the course of the study (Port insertion, thoracenteses or pericardiocenteses etc are acceptable)
- Minor surgical procedures such as fine needle aspirations or core biopsies within 7 days prior to enrollment
- Pregnant (positive serum pregnancy test) or lactating
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to enrollment
- Serious, non-healing wound, ulcer, or recent non-pathologic bone fracture. Bone fractures must be healed.
- Known hypersensitivity to any component of bevacizumab.
- Inability to comply with study and/or follow-up procedures

5.0 Discontinuation of Subjects from Treatment or Assessment

5.1 Criteria for Discontinuation

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject who is at any time free to discontinue participation in the study, without prejudice to further treatment.
- Incorrect enrollment of the subject
- Death
- Administration of radiotherapy, non-protocol chemotherapy, biological therapy or major surgical intervention during the trial
- Subject lost to follow-up
- Objective progression of disease
- Clinical or symptomatic deterioration
- Need for a third dose reduction of erlotinib
- Significant toxicities precluding study continuation:
    - Grade 4 hypertension or Grade 3 hypertension not controlled with medication
    - Reversible posterior leukoencephalopathy syndrome (RPLS)
    - Grade $\geq$ 2 pulmonary or CNS hemorrhage or any grade 4 hemorrhage, symptomatic Grade 4 venous thromboembolic event, requiring full dose warfarin or equivalent (i.e., unfractionated or low molecular weight heparin)
    - Nephrotic syndrome
    - Any grade arterial thromboembolic event
    - Grade 4 CHF
    - Gastrointestinal perforation
    - Gastrointestinal fistula formation, tracheoesophageal or other non-GI Grade 4 fistula formation
    - Bowel obstruction that has not fully recovered despite medical or surgical intervention
    - Wound dehiscence requiring medical or surgical intervention
    - Interstitial Lung Disease (ILD)
    - All Grade 4 events thought to be related to bevacizumab by the investigator
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- Treatment interruption of one or both study drugs for more than three weeks (ie 1 cycle)
- Full dose anticoagulation therapy

Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible.

5.2 Definition of DLT

For the purposes of this study the following events would be considered DLT:

- Any grade 4 hemorrhagic events
- Grade 4 hypertension or hypertensive encephalopathy,
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Any arterial thromboembolic events
- Any ***attributable*** grade 5 toxicity
- Grade ≥ 2 pulmonary or CNS bleeding
- Grade 4 CHF
- Clearly attributable interstitial lung disease occurring on treatment

6.0 Treatments

6.1 Bevacizumab

6.1.1 Bevacizumab formulation (supplied by Genentech)

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 5-cc (100-mg), 20-cc (400-mg), and 50-cc (1000-mg) glass vials containing 4 mL, 16 mL, or 40 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.
For further details and molecule characterization, see the bevacizumab Investigator Brochure.

6.1.2 Bevacizumab Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (Ozcan et al., 2006; Glusker et al., 2006).

Reversible Posterior Leukoencephalopathy Syndrome: There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms of headache, altered mental function, seizures, and visual disturbances / cortical blindness with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, management of specific symptoms, and discontinuation of bevacizumab. (Glusker et al. 2006; Ozcan et al. 2006).

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of Bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

In study AVF2107g, none of the 118 patients receiving bolus-IFL plus placebo, three of 158 patients (2%) receiving bolus-IFL plus bevacizumab, and two of 50 (4%) patients receiving 5-FU/LV plus bevacizumab who had a 24-hour collection experienced grade 3 proteinuria (> 3.5 g protein/24 hr). Rare events of nephrotic syndrome have occurred, and bevacizumab should be discontinued in patients with nephrotic syndrome.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous Thromboembolism (including deep venous thrombosis pulmonary embolism, and thrombophlebitis: In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of **venous TE** events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). There was also a higher rate of **arterial TE** events (3% vs. 1%) such as myocardial infarction, transient ischemia attack, cerebrovascular accident/stroke and angina/unstable angina**.** A pooled analysis of the rate of arterial TE events from 5 randomized studies (1745 patients) showed that treatment with chemotherapy plus bevacizumab increased the risk of having an arterial TE event compared with chemotherapy alone (3.8% vs. 1.7%, respectively) (Skillings et al., 2005). Furthermore, subjects with certain baseline characteristics (age ≥ 65 years and/or a history of a prior arterial TE event) may be at higher risk of experiencing such an event. . See the bevacizumab Investigator Brochure for additional information on risk factors.

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

The incidence of NCI-CTC Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; no fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure). In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

Arterial Thromboembotic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of

patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation: Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%–1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of

pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone (Scappaticci et al., 2005). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-associated hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, and/or tumors located in the center of the chest in close proximity to major blood vessels and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit.

In ECOG-conducted study E4599, in which squamous cell carcinoma was excluded, the rate of any type of Grade $\geq$ 3 hemorrhage was 1.0% in the control arm (carboplatin/paclitaxel) versus 4.1% in the carboplatin/paclitaxel + bevacizumab arm[23].

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Mucocutaneous Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment and most patients showed improved symptoms and/or left ventricular function following treatment. CHF has been reported in bevacizumab clinical trials and may be increased in incidence in patients with prior exposure to anthracyclines or prior irradiation to the chest wall. In a phase III trial (AVF2119g) of capecitabine with or without bevacizumab for metastatic breast cancer, 7 subjects (3.1%) who received capecitabine plus bevacizumab developed clinically significant CHF compared with 2 subjects (0.9%) treated with capecitabine alone; of note, all subjects in this trial had had prior anthracycline treatment. In addition, 2 subjects had a left ventricular ejection fraction < 50% at baseline and 2 others had prior left chest wall irradiation.

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm.

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracycline exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A recently published phase II study in subjects with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or decreases to <40% in left ventricular ejection fraction) of 48 subjects treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but one of these subjects had significant prior exposure to anthracyclines as well (Karp et al., 2004). Other studies are ongoing in this patient population. Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA or ECHO with a normal ejection fraction.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone[23].

Additional Safety Signals:

Other safety concerns seen to date—asthenia, pain, headache, fever, chills, rash, infection, epistaxis, and mouth ulceration—are not thought to be clinically significant in that they rarely or never required treatment or study drug discontinuation. An additional SAE reported in patients receiving bevacizumab is Nasal Septum Perforation.

Non-Gastrointestinal fistula formation has been reported in patients treated with bevacizumab (< 0.3%) some with fatal outcome. Permanent discontinuation of bevacizumab in patients with fistula formation involving any internal organ is recommended in a recent addition to the WARNINGS section of the Avastin label.

If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk after surgery).

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

6.1.3 Bevacizumab Dosage and Administration

Bevacizumab will be given at a dose of 15 mg/kg IV on day 1 of each 21 day cycle.

Bevacizumab will be diluted in 0.9% Sodium Chloride Injection, USP, to a total volume of 100 mL. Administration will be as an IV infusion. Anaphylaxis precautions should be observed during study drug administration. The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes.

6.1.4 Bevacizumab Storage

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

6.1.5 Bevacizumab Dose Modification and Toxicity Management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Refer to Table 1 for dose delays.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment on study should be discontinued.

Infusion Reaction Related to Bevacizumab:

Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 3.0 Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment and removed from the study. Document the reason for removal as hypersensitivity/bevacizumab.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 1. Infusion reactions are described in section 6.1.3

Regardless of the reason for holding bevacizumab treatment, including the events in Table 1, the maximum allowable length of treatment interruption is three weeks. If > three weeks, discontinue treatment. Treatment with erlotinib will continue during this period. Protocol treatment will discontinue if any of the drugs are held for more than three weeks.

Table 1 Bevacizumab Dose Management Due to Adverse Events	
Event	**Action Taken**
Hypertension	
Grade 1 or 2	No dose modifications
Grade 3	Hold bevacizumab and initiate additional or different anti-hypertensive therapy. Erlotinib may be continued during the hold interval. Check BP weekly and resume bevacizumab once BP controlled to $\leq$ 150/100. The day bevacizumab is resumed will be day 1 of the next cycle. Count the days that erlotinib was continued as part of the prior cycle. If not controlled with medication within 3 weeks, discontinue study treatment phase. May continue on treatment with grade 3 hypertension once controlled.
Grade 4 (including RPLS confirmed by MRI or hypertensive encephalopathy)	Discontinue study treatment phase
Hemorrhage	
Grade 1 Pulmonary or CNS hemorrhage	Hold bevacizumab and evaluate for source of bleed. Erlotinib may continue. If resolved within 1 week, and no source, resume full-dose bevacizumab. If recurrent, discontinue study treatment phase. For recurrent epistaxis that is mild and does not require intervention, treatment may continue.
Grade $\geq$ 2 Pulmonary or CNS hemorrhage	Discontinue study treatment phase. In subjects with hemoptysis, consider early use of bronchoscopy in identify the site of bleeding.
Other/non-pulmonary or non-CNS grade 1 or 2 events of hemorrhage	No dose modifications
Grade 3 Non-pulmonary or CNS hemorrhage	Hold bevacizumab. May continue erlotinib. In subjects with bleeding, consider full hemostasis evaluation, which may include additional INR, bleeding time measurements, and platelet aggregation, etc. In subjects with GI bleeding, consider stool guaiacs and early use of endoscopy or other studies to identify the location of the bleeding. Subjects who are also receiving full-dose anticoagulation will be discontinued study treatment phase. All other subjects will have bevacizumab held until all of the following criteria are met: o The bleeding has resolved and hemoglobin is stable +/- 1 g/dl over 24 hours. o There is no bleeding diathesis that would increase the risk of therapy. o There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued study treatment phase.

Table 1 (continued) Bevacizumab Dose Management Due to Adverse Events:	
Event	**Action Taken**
Grade 4	Discontinue study treatment phase.
Venous Thrombosis	
Grade 1 or 2	No dose modifications
Grade 3 or Grade 4	Hold bevacizumab (continue erlotinib). If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Arterial Thromboembolic event [new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event]	
Any Grade	Discontinue study treatment phase
Event	
Congestive Heart Failure (Left ventricular systolic dysfunction)	
Grade 1 or 2	No dose modifications
Grade 3	Hold bevacizumab until resolution to Grade ≤ 1. May continue erlotinib at investigator's discretion.
Grade 4	Discontinue study treatment phase
Proteinuria	
Grade 1 or 2	No dose modifications
Grade 3 (UPC > 3.5, urine collection> 3.5 g/24 hr)	Hold Bevacizumab until ≤ Grade 2 A UPC ratio of ≤3.5 or ≤ 3.5 gm/dL in a 24 hr. urine collection
Grade 4	Discontinue study treatment phase
Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Erlotinib to be held if subject is NPO. Patient may restart bevacizumab upon complete resolution. Erlotinib can be restarted when oral intake is permitted (may dissolve tablets in distilled water) if within 3 weeks.
Grade 3/4	Hold bevacizumab for complete obstruction. If surgery is necessary patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion

Table 1 (continued) Bevacizumab Dose Management Due to Adverse Events:	
Event	**Action Taken**
Gastrointestinal perforation	
Any Grade	Discontinue study treatment phase
Fistula	
Any grade (TE fistula)	Discontinue study treatment phase
Grade 4 fistula	Discontinue study treatment phase
Reversible Posterior Leukoencephalopathy Syndrome (confirmed by MRI)	
Any Grade	Discontinue study treatment phase
Nasal Septum Perforation	
Any Grade	Discontinue study treatment phase
Wound dehiscence Requiring medical or surgical therapy	Discontinue study treatment phase
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to $\leq$ Grade 1
Grade 4	Discontinue study treatment phase

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 4.2) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 5.0). Specific monitoring procedures are as follows:

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure is required. For blood pressure $\geq$ 150/100 mm/Hg on the day of treatment with bevacizumab, which can not be controlled with standard antihypertensive therapy, treatment with bevacizumab must be withheld.
- If patients on treatment with bevacizumab require elective major surgery, they must be taken off study (section 5.1). It is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk after surgery). It is the treating physician's discretion whether or not to resume bevacizumab but if

treatment is resumed it will be off study and no further drug will be supplied through this study.

- In patients with bleeding, hemostasis evaluation should be performed as clinically indicated.
- Proteinuria will be monitored through urinary protein/creatinine ratio or dipstick performed at least every 6 weeks
- Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution or deemed irreversible.

Erlotinib will continue as per protocol guidelines until toxicities resolve and bevacizumab is continued or until the patient is removed from the study.

6.2 Erlotinib (Tarceva) (supplied by Genentech)

6.2.1 Formulation

In addition to the active ingredient, Tarceva (erlotinib hydrochloride), tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

Tablets containing 25 mg, 100 mg, and 150 mg of erlotinib are available. The oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. Each bottle will contain 30 tablets, a quantity sufficient for 4 consecutive weeks of dosing, with overage.

For further details, see the erlotinib Investigator Brochure.

6.2.2 Erlotinib Safety Profile

Common adverse events associated with erlotinib administration include rash and diarrhea. Other common adverse events include nausea/vomiting, mucositis/stomatitis, headache, and fatigue.

A rash occurred in 75% of erlotinib-treated NSCLC patients enrolled in BR.21. Similar incidence of rash have occurred when erlotinib was administered concurrently with chemotherapy including gemcitabine, paclitaxel/carboplatin, and gemcitabine/cisplatin. A papular, pustular rash manifesting most often on the face and upper trunk was common across all studies, but rash was rarely the cause of study drug discontinuation. Other dermatologic manifestations reported in clinical studies or postmarketing use of erlotinib include nail changes, paronychia, painful fissures or cracking of the skin on the hands and feet, and hair growth abnormalities (alopecia, thinning hair, eyelash/eyebrow changes, hirsutism).

Wearing of contact lenses while receiving erlotinib therapy is not recommended. The incidence of diarrhea in BR.21 was 54% of erlotinib-treated NSCLC patients. The

median time to onset of skin rash was 8 days and median time to occurrence of first diarrheal symptom was 9 days.

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

Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia or concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (eg, pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration.

Erlotinib is both protein bound (92%–95%) and metabolized by hepatic cytochromes CYP3A4 and CYP3A5 and pulmonary cytochrome CYP1A1. Therefore, a potential for drug–drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 inhibitors/inducers.

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

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

Erotinib clearance can be induced by smoking via CYP1A2 induction. Potential drug-drug interaction is expected when erlotinib is taken with CYP1A2 inducers or inhibitors. In a single-dose study in healthy volunteers, the AUC was reduced by 64% in smokers when compared with nonsmokers. In BR.21, current smokers achieved erlotinib steady-state trough plasma concentrations, which were approximately 2-fold less than the former

smokers or patients who had never smoked. This effect was accompanied by a 24% increase in apparent erlotinib plasma clearance. Similarly, in a Phase I (N=35) dose escalation PK study in NSCLC patients who were current smokers, Pka at steady-state indicated a dose proportional increase in erlotinib exposure when the erlotinib dose was increased from 150mg to 300mg. However, the exact dose to be recommended for smokers is unknown. These data suggest that patients who continue to smoke may be under dosed when treated with the current approved erlotinib dosage of 150mg, therefore, warranting consideration of dose escalation. Patients should be advised to stop smoking. If patients continue to smoke, a cautious increase in the dose of erlotinib, not exceeding 300mg/day may be considered while monitoring the patient's safety. If patients decide to stop smoking while on a higher dose, then the dose should be reduced immediately to the indicated starting dose. Efficacy and long-term safety (>14 days) of a higher dose than the recommended starting dose has not been established in patients who continue to smoke. Pretreatment or co-administration of erlotinib did not alter the clearance of a prototypical CYP3A4 substrate, midazolam. Therefore, significant metabolic interactions with other CYP3A4 substrates are unlikely. However, the oral bioavailability of midazolam decreased by up to 24% following erlotinib treatment, which was not attributed to a metabolic interaction.

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

Co-administration of erlotinib with an inhibitor of CYP3A4 metabolism (ketoconazole, 200 mg po BID for 5 days) resulted in increased exposure to erlotinib as measured by an 86% increase in median erlotinib AUC and a 69% increase C_{max}, compared with administration of erlotinib alone.

Induction of CYP3A4 metabolism by a known enzyme inducer (rifampin, 600 mg po QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, compared with administration of erlotinib alone. However, the effect of rifampin on C_{max} was negligible. In another study, rifampicin pretreatment followed by co-administration of rifampicin with a single 450 mg dose of erlotinib resulted in a mean erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg erlotinib dose in the absence of rifampicin treatment. Therefore, a potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are potent CYP3A4 inhibitors or inducers.

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

Cardiovascular Effects: Myocardial infarction
Dermatologic Effects: Rash
Gastrointestinal: Diarrhea, gastrointestinal hemorrhage, stomatitis, mucositis, anorexia, nausea, vomiting, weight loss
Hematologic Effects: Deep venous thrombosis, neutropenia, and anemia, microangiopathic hemolytic anemia, with thrombocytopenia
Hepatic Effects: Acute hepatitis, hyperbilirubinemia, increased liver enzymes
Neurologic Effects: Cerebrovascular accidents, headache
Ophthalmic Effects: Conjunctivitis, Keratitis, Keratoconjunctivitis sicca, Lower eyelid ectropion, Trichiasis, Trichomegaly
Renal Effects: Renal failure, renal impairment
Respiratory Effects: Cough, dyspnea, epistaxis, interstitial lung disease
Other: Fatigue, infectious disease, teratogenicity/effects in pregnancy/breastfeeding

Based on clinical results, rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting and headache were the most frequently observed undesirable effects following exposure to single-agent erlotinib. Patients receiving erlotinib in combination with various chemotherapy agents have generally experienced the same type of AEs as with either agent alone. AEs considered study drug related that appear to occur more frequently when erlotinib is administered with chemotherapy, regardless of regimen, include nausea, vomiting, stomatitis, and anemia.

General Plan to Manage Safety Concerns:

A number of measures will be taken to ensure the safety of patients participating in this trial, addressed through exclusion criteria and routine monitoring. Patients will be evaluated for adverse events at each study visit for the duration of their participation in the study and for a minimum of 30 days after the discontinuation of erlotinib.

Skin toxicities will be monitored by routine physical examination and managed symptomatically. The following agents may be used to treat rash: diphenhydramine, topical or oral corticosteroids, and topical (clindamycin) or oral antibiotics (tetracycline, minocycline, doxycycline). Topical drying agents are not recommended.

Diarrhea will be monitored and managed symptomatically. Guidelines for management include administration of loperamide and erlotinib dose reduction/interruption as described in Section 6.2.6.2.

Although quite rare, ILD can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often provided. Erlotinib should not be restarted in those patients suspected of having drug-related ILD. See Section 6.2.6.3 and Table 4 for management guidelines, including erlotinib dose interruption.

Liver function abnormalities, including elevated serum ALT, AST, and/or bilirubin, have been observed infrequently with single-agent erlotinib and occasionally with erlotinib in combination with concomitant chemotherapy. Treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with erlotinib. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range.

Women of childbearing potential should have a negative pregnancy test prior to starting therapy with erlotinib. Men and women should use adequate contraceptive methods during and for at least 2 weeks after erlotinib therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. If a patient becomes pregnant despite precautions, she should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

It is not known whether erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of erlotinib on infants have not been studied, women should be advised against breast-feeding while receiving erlotinib therapy.

6.2.3 Dosage and Administration

Erlotinib will be self-administered in an open-label, unblinded manner to all patients enrolled in the study. During the treatment period, patients will receive erlotinib 150 mg/day. Tablets should be taken at the same time each day with 200 mL of water at least 1 hour before or 2 hours after a meal. Patients who are unable to swallow tablets may dissolve the tablets in distilled water for administration.

Dose reductions for adverse events will be permitted (see Section 6.2.6). Treatment is continued daily until disease progression or other reason for termination of study therapy (see Section 5.1).

6.2.4 Drug Ordering and Accountability

All study drug required for completion of this study will be provided by OSI-Pharmaceutical (manufacturer), in partnership with Genentech and distributed through Biologics Inc.

Following submission and approval of the required regulatory documents, the initial order may be placed. Biologics drug order forms and ordering procedure will be presented at the site initiation meeting.

It is the responsibility of the Investigator to ensure that a current record of investigational

product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

Amount received and placed in storage area.
Amount currently in storage area.
Label ID number or batch number.
Dates and initials of person responsible for each investigational product inventory entry/movement.
Amount dispensed to and returned by each patient, including unique patient identifiers.
Amount transferred to another area for dispensing or storage.
Non-study disposition (e.g., lost, wasted, broken).

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs.

6.2.5 Storage

Erlotinib tablets will be supplied for clinical trials in white, high-density polyethylene (HDPE) bottles with child-resistant closures and should be stored at temperatures between 15°C and 30°C (59°F and 86°F).

6.2.6 Dose Modification and Toxicity Management

Dose reduction or interruption of erlotinib for toxicity may take place at any time during the study. The patient will remain on bevacizumab until toxicities resolve and erlotinib is resumed or until the patient is removed from the study. Toxicity grading is based on NCI-CTCAE, v 3.0. Dose level reductions are presented in Table 2. If patients do not tolerate the second dose reduction, erlotinib is to be discontinued and the patient removed from the study.

Regardless of the reason for holding treatment, the maximum allowable length of treatment interruption is 3 weeks. If > 3 weeks, discontinue study treatment phase.

Table 2

Erlotinib Dose Level Reductions		
Starting Dose	First Reduction	Second Reduction
150 mg/day	100 mg/day	50 mg/day

6.2.6.1 Dermatologic

Management of a tolerable Grade 2 or 3 rash should include continuation of erlotinib at the current dose and symptomatic management. If skin rash is intolerable, dose reduction according to Table 4 should be considered. When skin toxicity improves by at least one grade level, the dose may be re-escalated to prior dose level as tolerated. In Phase II trials, this approach enabled dose re-escalation for the majority of patients requiring dose reduction for skin toxicity. Patients

experiencing Grade 4 skin toxicity should be discontinued from study treatment.

Skin toxicities will be monitored by routine physical examination and managed symptomatically. Because secondary bacterial infections are common and can lead to more serious complications, topical, or systemic antibiotics may be considered. Anecdotally, topical or a short course of systemic corticosteroids can be helpful. See Table 3 for management guidelines, including erlotinib dose reduction/interruption.

6.2.6.2 Gastrointestinal

Diarrhea will be monitored and managed symptomatically. Guidelines for management include administration of loperamide and erlotinib dose reduction/interruption as described in Table 3.

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

6.2.6.3 Pulmonary

Although quite rare, ILD can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, erlotinib treatment should be interrupted and the patient should receive appropriate medical evaluation. Although there is no proven therapy, systemic corticosteroids are often provided. Erlotinib should not be restarted in those patients suspected of having drug-related ILD. See Table 3 for management guidelines, including erlotinib dose interruption. If diagnosed with ILD, the patient will be removed from the study.

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

NCI-CTCAE (v 3.0) Grade	Tarceva Dose Modification	Guideline for Management
Diarrhea		
Grade 1	None	Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours)
Grade 2	None, unless grade 2 diarrhea persists >48 hours despite optimal medical management, reduce one level.	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours)
Grade 3	Interrupt then reduce by one dose level. Erlotinib should not be re-escalated.	See above treatment. Interrupt until resolution to Grade ≤1, restart at next reduced dose. Other interventions as medically indicated.
Grade 4	Discontinue study treatment.	As medically indicated.
Pulmonary Events		
All Grades	Temporarily interrupt erlotinib for diagnostic evaluation. If assessed as related to erlotinib, discontinue from study treatment. Otherwise resume at prior dose level once resolved to ≤ grade 1.	Unexplained dyspnea, either new or progressive, should be aggressively evaluated.
Pulmonary Events if possibly ILD		
All grades	Erlotinib should not be restarted in those patients suspected of having drug-related ILD. The patient should be removed from the study.	Unexplained dyspnea, either new or progressive, should be aggressively evaluated. Although there is no proven therapy, systemic corticosteroids are often provided.

Table 3 (continued)		
Rash		
Grade 1 and 2 Tolerable rash.	None	Any of the following: oral antibiotics minocycline, tetracycline, doxycycline, topical clindamycin, diphenhydramine,or oral corticosteriods at discretion of investigator
Grade 3 Intolerable rash	Consider interruption and or one dose level reduction, if unresponsive to symptomatic management. Re-escalation is allowed.	Manage as described above
Grade 4	Discontinue study treatment.	Manage as described above

6.2.6.4 Other treatment related adverse events

Treatment with both agents should be held for any other grade 3 or 4 toxicities except for alopecia, until resolution to grade ≤ 1. Erlotinib will be reduced by one dose level.

7. 0 Concomitant and Excluded Therapies

Use of anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study.

Use of concurrent investigational agents is not permitted.

There are potential interactions between erlotinib and CYP3A4 inhibitors and CYP3A4 promoters. Although caution and careful monitoring are recommended when use of these compounds is necessary, use of these compounds does not exclude patients from participating in this trial (see Appendix C for a list of CYP3A4 inhibitors/inducers).

Grapefruit juice is a CYP3A4 inhibitor, therefore, consumption of grapefruit or grapefruit juice should be avoided during erlotinib treatment.

Patients who are taking erlotinib with an inhibitor of both CTP3A4 and CYP1A2 like ciprofloxacin, a dose reduction of erlotinib should be considered if severe adverse reactions occur.

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure of erlotinib (AUC) by 46% and the maximum concentration (C_{max}) by 61%. There was no change

to Tmax or half-life. Therefore, drugs that alter the pH of the GI tract may alter the solubility of erlotinib and hence its bioavailability.

Concomitant use of erlotinib with proton pump inhibitors should be avoided if possible. The use of antacids may be considered in place of histamine 2 receptor blockers (H2 blockers) or proton pump inhibitors in patients receiving erlotnib. However, no clinical study has been conducted to evaluate the effect of antacids on erlotinib pharmacokinetics. If an antacid is necessary, the antacid dose and the erlotnib dose should be separated by several hours.

The exposure to erlotinib (AUC) increased to a moderate extent, by 39%, and the maximum concentration (C_{max}) by 17%, when erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2. Patients who are taking erlotinib with an inhibitor of both CYP3A4 and CYP1A2 like ciprofloxiacin, a dose reduction of erlotinib should be considered if severe adverse reactions occur.

Erlotinib clearance can be induced by smoking via CYP1A2 induction. Potential drug-drug interaction is expected when erlotinib is taken with CYP1A2 inducers or inhibitors. Patients who continue to smoke may be under dosed when treated with the current approved Tarceva dosage of 150mg, therefore, patients should be advised to stop smoking.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on erlotinib. Patients taking warfarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

Low-dose aspirin (≤ 325 mg/d) may be continued in subjects at higher risk for arterial thromboembolic disease. Subjects developing signs of arterial ischemia or bleeding on study should be evaluated for possible bevacizumab discontinuation per Table 1, Bevacizumab Dose Management Due To Adverse Events.

Treatment with hormones or other chemotherapeutic agents will result in the patient's removal from the study, except for steroids administered for adrenal failure, septic shock, or as temporizing measure for symptomatic pain or breathing, rash, or at the treating physician's discretion for symptom management, or hormones administered for non-disease related conditions, e.g., insulin for diabetes. Glucocorticosteroids may be used as antiemetics and megestrol acetate may be used for appetite.

Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The use of erythropoietin *(i.e., Epogen, Procrit)* is permitted.

Bisphosphonates for bone pain and colony stimulating factors (i.e., G-CSF, GM-CSF, etc.) may be used according to ASCO guidelines.

8.0 Clinical and Laboratory Evaluations

8.1 Pre-Treatment Evaluation

Epidermal growth factor receptor testing of archival tissue should be done if sufficient tissue is available. Results are not needed prior to initiation of treatment.

The following evaluations should take place within 14 days of enrollment and may be used for C1D1 evaluations:

- CBC with differential
- Biochemistry including: electrolytes, renal function, liver function, LDH, Bilirubin
- Serum B-HCG for WOCBP
- PT/PTT/INR
- Urine protein:creatinine ratio (See appendix F)
- Charlson Co-Morbidity Index to be performed by treating MD or designee. (See appendix H)
- FACT-L Assessment (See appendix G)

The following evaluations should take place within 28 days of enrollment

- CT/MRI brain, preferably with contrast
- CT scan chest/abdomen, preferably with contrast (or MRI if abdominal CT not diagnostic)
- PET scan in addition to CT scans is recommended by not mandatory

8.1.1 Physical examinations

Methods of assessment
Full physical examinations will be performed within 14 days of enrollment and will include performance status (appendix D), heart rate and blood pressure, weight, height, concurrent medications, review of systems.

8.2 Evaluations During Treatment

Performed on the first day of each three-week cycle.

- Urine protein:creatinine ratio every other cycle (every 6 weeks) (may be done up to 7 days before D1 if site unable to obtain same day results). On treatment testing may be done by urine dipstick however if > 1+ treatment must be held until laboratory results are available.
- CBC with differential (may be done within 24 hours prior to D1 if site unable to obtain results in time to treat)
- Biochemistry including: electrolytes, renal function, liver function, LDH, Bilirubin (may be done up to 7 days before D1 if site unable to obtain same day results)
- PT/PTT/INR if on low dose coumadin
- Full physical exam with weight (calculate BSA each cycle), vital signs including blood pressure, performance status, concurrent medication and review of systems

- Adverse Event (with CTC v. 3.0 grading and causality) recording/monitoring
- CT scans chest/abdomen after every 3rd cycle of treatment.
- FACT-L Assessment after every two cycles of treatment. May be completed on day one of subsequent cycle. The FACT L can be done after every third cycle of therapy; after first 6 months.

8.3 End of study

Subjects who discontinue study treatment should be seen and assessed by an investigator(s). The reason for withdrawal and the date of withdrawal must be documented. If possible, any diary cards, questionnaires (e.g. for Quality of Life assessments) and investigational products (erlotinib) should be returned by the subject. Patient should undergo the following at the time of discontinuation from the study:

- Full physical exam with performance status, vital signs, weight, review of systems
- CBC with differential
- Biochemistry including: electrolytes, renal function, liver function, LDH, Bilirubin
- Urine protein:creatinine ratio
- Attributable Adverse Event (with CTC grading) recording/monitoring until resolved to ≤ grade I
- FACT-L Assessment

If the reason for withdrawal from the trial is the death of the subject, the two options for categorizing withdrawal are either progressive disease or an adverse event (AE); more than one AE may be documented as a reason for withdrawal. Only one event will be captured as the cause of death. Note that death is an outcome and not an AE.

All deaths that occur within the trial period or within 30 days after administration of the last dose of trial drug must be reported primarily for the purposes of serious adverse event (SAE) reporting; however, deaths due unequivocally to progression are not SAE's.

All subjects who have new or worsening CTC grade 3 or 4 laboratory values that are deemed to be at least possibly related at the time of withdrawal must have further tests performed and the results recorded appropriately until the lab values have returned to CTC grade 1 or 2, unless these values are not likely to improve because of the underlying disease. In these cases, the investigators must record their opinions in the subject's medical records. Laboratory abnormalities should **not** be reported as serious adverse events unless any criterion for a SAE is fulfilled, the laboratory abnormality causes the subject to discontinue from the study, or the investigator insists the abnormality should be reported as an attributable AE. At withdrawal all on-going study-related toxicities and SAEs must be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

Patients should be seen in the clinic or contacted by telephone to determine if any serious or non-serious adverse events have occurred within 30 days (±3 days) of termination of study treatment.

8.4 Long Term Follow up Evaluations

Evaluations to be completed every three months for two years, then every six months for three years then annually until death.

- Full physical exam with weight, vital signs, performance status, concurrent medication and review of systems
- Attributable Adverse Event (with CTC grading) recording/monitoring until resolved to ≤ grade I
- CT scans chest/abdomen repeated every 12 weeks in patients who have not progressed.

9.0 Registration

Subjects may be registered from 9:00 am to 5:00 pm by calling the FER Study Coordinator at 215-728-2451. The investigator or designee will then fax the completed registration form and eligibility checklist to 215-728-4784. FER will notify the site by phone and fax when eligibility is confirmed and the sequence number has been assigned. Subjects must be registered and have received a sequence number assigned by FER prior to the initiation of treatment. Treatment should start within 14 days of registration. If ≥ 30 days from time informed consent form (ICF) signed and subject is registered, subject will need to re-sign and date ICF as will treating MD. The following forms must be completed at the time of registration:

- Signed and dated informed consent form
- Signed and dated HIPAA consent form
- Registration form
- Signed eligibility checklist

Exceptions to the current registration policies will not be permitted as well as:

- Late registrations (after initiation of treatment)
- Exceptions to eligibility requirements (unless by approved waiver)
- Participation by an institution/member not identified as eligible
- Non-Compliance with Regulatory paperwork

10.0 Data Safety Monitoring Plan

All adverse events will be summarized 1) without regard to causal relationship and 2) by causal relationship to study drugs, based on the Investigator's opinion. Worst toxicity grades per patient will be tabulated for selected adverse events and laboratory measurements. Any serious adverse event or adverse event resulting in premature and permanent discontinuation of any study drug will be described in detail.

Adverse events and other symptoms will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

A Data Safety Monitoring Plan has been implemented to monitor safety parameters during the

study. Ongoing monitoring will confirm proper conduct of this study for each subject and identify any protocol violations and unreported adverse events in a timely manner. Any events determined to be significant will be reported immediately to the principal investigator. FER administrative staff will review data every six months with the principal investigator or his designee. Data will be collected from individual case report forms (CRF) once the CRFs have been monitored and all queries are resolved. The semiannual review will include complete accrual listing demographic information, response, toxicity tables, and summaries of incidence severity and resolution of adverse events, including laboratory results abnormalities, summary of any pertinent findings from monitoring/auditing visits and a description of all known or suspected protocol violations.

Each participating practice must designate a single on-site principal investigator with primary responsibility for the conduct of the study in his practice. This site specific principal investigator is responsible for identification of all adverse events at their site and must verify that appropriate procedures are being followed. SAEs experienced by a subject participating in a clinical trial must be reported according to section 13.0 Adverse Event Reporting and Definitions. FER is responsible for collecting and reporting serious adverse events to the study principal investigator and appropriate regulatory authorities and to other participating sites for IRB submission. Each practice must designate an IRB for this study and follow any by-laws regarding the use of an IRB set forth by the terms of their employment or determined by the institution in which they practice. Investigators must supply their designated IRB with ongoing progress reports for the study and a formal review of each study will be conducted at least every 364 days or more frequently as designated by the IRB. The IRB may suspend, terminate or restrict the study as appropriate.

FER will manage the flow of documents to participating sites and external agencies (including reports of serious adverse events) to facilitate ongoing and timely review of the protocol. FER will monitor the medical and study records of each participant accrued at each site throughout the course of the study. All serious adverse events (SAEs) will be reviewed on a real time basis first by the site PI and subsequently by Dr. Borghaei. Regular teleconferences may be conducted with all principal investigators or their designees. During these meetings, the participants will review documents summarizing baseline demographic characteristics, retention and disposition of participants, QA issues, regulatory issues, AEs and SAEs, and efficacy (response rates, time-to-progression). FER will supplement these meetings with routine written summary updates which will be distributed to the participating sites.

Grade 4-5 serious adverse events must be reported to FER within 24 hours of awareness of the event (please refer to section 13). FER will report this information immediately to the principal investigator, and appropriate regulatory authorities. Participating site PIs will be notified according to section 13.0.

11.0 Statistical methods and determination of sample size

A phase II investigation will be conducted in patients with advanced stage non small cell lung cancer, chemo-naïve patients, aged 65 years and older with PS 0-1

11.1 Primary endpoint: Progression Free Survival

PFS will be the primary endpoint. We will test the null hypothesis that median PFS is 3 months versus the alternative that it is at least 5 months. A one sample, one-sided test based on exponentially distributed survival times will have 90% power and 5% type I error for a study of 33 evaluable patients accrued over a period of 24 months and followed for an additional 12 months. Follow up on all patients for progression and survival will continue until death.

Toxicity is monitored for possible early stopping. If, at any point in time 5 patients experience attributable DLTs (DLT defined in section 5.2) among the first 17 patients treated, the study will be stopped. If at any later point any 8 patients experience attributable DLTs, treatment will be regarded as too toxic. If the chance of DLT is at least 30% then the chance of early stopping is at least 61% and the chance of declaring the treatment too toxic is at least 84%. If the chance of DLT is at most 15% then the chance of early stopping, in error, is 9.9% and the overall type I error is 15.5%. Early stopping, here, does not mean that accrual is stopped until the first 17 patients complete 12 months of follow up. Since toxicity can occur at any time, 5 attributable DLTs among the first 17 patients requires stopping the study even if all 33 patients have started but before they complete treatment. All patients must, in that case, or in case of 8 attributable DLTs, experienced by any patient, be taken off study.

One year and overall survival are secondary endpoints. We will test the null hypothesis that one year survival is at most 20% versus the alternative that it is at least 35%. A one-sided test based on the exponential distribution of survival time will have 86% power and 10% type I error to make this distinction.

11.2 Secondary Endpoints

11.2.1 Toxicity

All toxicities relating to study drugs will be recorded for each patient during the study. Adverse Events will be recorded.

11.2.2 Time to Progression

Time to Progression will be assessed from the start of study treatment to the date when objective disease progression is observed. Subjects without documented objective progression at the time of the final analysis will be censored at the date of their last tumor assessment.

11.2.3 Overall Survival

Survival will be assessed from the start of study treatment to the date of subject death, due to any cause, or to the last date the subject was known to be alive. We will measure median survival, one-year and two-year survival rates.

11.3 Tertiary Objective

11.3.1 Quality of Life

At every other cycle, while patients are on-study or after the third cycle if the patient is on therapy for greater than 6 months; the FACT-L questionnaire will be used to assess quality of life. Quality of Life will be evaluated graphically and with descriptive statistics. Changes over time will be noted.

12.0 Efficacy Measurement

12.1 Response Evaluation Criteria in Solid Tumors (RECIST)

The Response Evaluation Criteria in Solid Tumors (RECIST) criteria will be used for objective tumor response assessment. See Appendix A for the timing of the assessments.

12.1.1 Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee[36]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

12.1.2 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.1.3 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

12.1.4 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 response.

12.1.5 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.2 Guidelines for Evaluation of Measurable Disease

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.
Lesions located solely in a previously irradiated area will only be considered measurable if there has been demonstrable progression in the region of prior irradiation since the time of radiation as defined by RECIST criteria.
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

12.3 Response Criteria

12.3.1 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 longest diameter (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

12.3.2 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) and/or 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
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 at a later time by the PI.

12.3.3 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 progressive disease the smallest measurements recorded since the treatment started). 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

Note: 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) before confirming the complete response status.

12.4 Confirmatory Measurement/Duration of Response

12.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for

response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

12.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.
Upon the subject's withdrawal, the investigator should assign an overall best response for the subject based on the definitions given in Appendix and his or her clinical judgment.

12.4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

12.4.4 Survival

Survival will be assessed from the start of study treatment to the date of subject death, due to any cause, or to the last date the subject was known to be alive.

12.4.5 Time to Progression

Time to Progression (TTP): will be assessed from the start of study treatment to the date when objective disease progression is observed. Death will be regarded as a progression event in those subjects who die before disease progression. Subjects without documented objective progression at the time of the final analysis will be censored at the date of their last tumor assessment.

12.5 Reporting of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (*Note*: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus an incorrect treatment schedule or drug administration

does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.

Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should be provided.

12.6 Patient-Reported Outcomes (PROs)

The methods for collecting subject/Patient Reported Outcomes (PRO) data are presented below. Functional Assessment of Cancer Therapy – Lung, Version 4 (FACT-L v. 4) (secondary endpoint)

12.6.1 Functional Assessment of Cancer Therapy-Lung (FACT-L)(Appendix G)

Methods of Assessment
Functional Assessment of Cancer Therapy – Lung, Version 4 (FACT-L v. 4) will be utilized for each patient prior to the start of therapy, on the first day of every other cycle, for the first 6 month, then after every third cycle of therapy and at the time of treatment discontinuation. Please see Appendix G for FACT-L questionnaire.

Administration of PRO questionnaires
Each center must allocate responsibility for *FACT-L administration* to a specific individual (e.g., a Research Nurse). The Fox Chase Cancer Center Extramural Research Program (FER) will provide training for relevant personnel in the administration of the FACT-*L* to help avoid the key problem of missing data. It is also important that the significance and relevance of the data are explained carefully to participating subjects so that they are motivated to comply with data collection[37].
The date of completion of each *FACT-L* should be documented.
The instructions for completion of the *FACT-L* are:

- It must be completed in private by the subject in their own time
- It must be completed by the subject before any investigations or discussions about their disease with the clinic staff
- The subject should not receive help from relatives, friends or clinic staff
- Only one answer to each question should be recorded
- Immediately following completion of *FACT-L*, the Research Nurse or appointed individual must collect and review the *FACT-L* for completeness. If items are missed, the form must be returned to the subject immediately for completion.

12.6.2 Collection of Records

The entire FACT-L will be collected. We will assess patient-specific changes over time based on the 7 item lung cancer subscale (LCS) and treatment outcome index (TOI) composed of the sum of physical well- being (PWB), functional well-being (FWB), and LCS scores.

12.6.3 Procedure for Missing Data

For each subscale, if less than 50% of subscale items are missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. Hence, missing data will be imputed. If at least 50% of the items are missing, that subscale also will be treated as missing. The reason for any missing data will be identified. If data are missing at random, the above techniques will be used. If there is evidence that the missing data is systematic, missing values will be imputed to ensure that any possible bias is minimized.

13.0 Adverse Event Reporting and Definitions

In the event of an adverse event the first concern will be for the safety of the subject.

Calculation or derivation of outcome variables
Any new conditions reported during the study will be documented as an AE. Only those findings that are in addition to the condition being treated will be documented as AEs, see Section 13 for recording of AEs.

If the patient is withdrawn from the trial due to death, the two options for categorizing withdrawal are either progressive disease or an adverse event (AE); more than one AE may be documented as a reason for withdrawal). Only one event will be captured as the cause of death. Note that death is an outcome and not an AE.

All deaths that occur within the trial period or within 30 days after administration of the last dose of trial drug must be reported primarily for the purposes of serious adverse event (SAE) reporting; however, deaths due unequivocally to progression are not SAE's.

Investigators are required to report to FER serious adverse event (SAE) as soon as possible.

13.1 Adverse Event (AE) Definitions

Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines January 2001)*.

Serious Adverse Event (SAE) is any sign, symptom or medical condition that emerges during protocol treatment or during a post-treatment follow-up period that (1) was not present at the start of study treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of study treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

13.1.1 Severity Ratings The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events Version 3.0 will be used to capture adverse events. Severity is expressed in numerical grade using the following definitions if the AE is not clearly specified in the CTC

Grade 1: Mild-noticeable to the patient, does not interfere with the patient's daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study drug.
Grade 2: Moderate-interferes with the patient's daily activities, possibly requires additional therapy, but does not require discontinuation of study drug.
Grade 3: Severe-severely limits the patient's daily activities and may require discontinuation of the study drug.
Grade 4: Life-threatening or disabling
Grade 5: Fatal

13.1.2 Relationship to Study Drug/Attribution

Definite –clearly related
Probably Related-the event occurs within a reasonable time period following drug administration or follows a known response for the drug and cannot be reasonably explained by known patient characteristics (including use of concomitant medications).
Possible –may be related
Unlikely –doubtfully related
Definitely Not Related - the event is not known to be caused by the study drug.
Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.
Unexpected Adverse Event is one not identified in nature, severity, or frequency in the Investigator's Brochure or the product package insert for the study drug.

13.2. Investigator Reporting Responsibilities:

1. Upon identification of an AE, the investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. Assessing Causality:
   Investigators are required to assess whether there is a reasonable possibility that the study treatment caused or contributed to an adverse event. The following general guidance may be used.
   - Yes: if the temporal relationship of the clinical event to study drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
   - No: if the temporal relationship of the clinical event to study drug administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

3. All AEs and SAEs will be recorded in the case report forms on the "AE/Toxicity Form" with details about the grade and attribution of each episode. The action taken with respect to the study drug and the patient's outcome should be recorded in the remarks section of the "Treatment Flow Sheet". All events will be recorded on case report forms each cycle until they resolve.

4. All SAEs will be recorded on "FDA Form 3500 MedWatch" and faxed to the Office of Extramural Research (FER) Study Manager at 215-728-4784. FER will submit to Genentech. After submitting the initial report it may be necessary to submit additional reports by the investigator should the event require further investigation. In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch 3500 form:

   - Treatment regimen (dosing frequency, combination therapy, lot numbers)
   - Protocol description (and number, if assigned)
   - Description of event, severity, treatment, and outcome, if known
   - Supportive laboratory results and diagnostics
   - Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

5. Follow-up information:
   Additional information may be added to a previously submitted report by any of the following methods:
   - Adding to the original MedWatch 3500 report and submitting it as follow-up
   - Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form
   - Summarizing new information and faxing it to FER with a cover letter including subject identifiers (i.e. D.O.B., initials, subject number), protocol description and number, if

assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report.)

6. Each investigator is responsible to report all AEs/SAEs to IRB following guidelines set by that IRB. FER reserves the right to request an event be reported to the IRB at their discretion. Copies of all documentation of events reviewed by the IRB must be sent to the FER Regulatory Coordinator.

   Sites are responsible for forwarding copies of documentation of IRB review of the event to FER regulatory coordinator at:
   50 Huntingdon Pike, Second Floor
   Rockledge, PA 19046
   Phone: 215-214-3773
   Fax: 215-728-4784

7. Timelines for Reporting SAEs to FER:
   - Unexpected Event: Grade 2-3 with possible, probable, or definite attribution requires written report to FER within 3 working days.
   - Unexpected Grade 4-5 regardless of attribution requires report to FER by phone/fax/e-mail within 24 hours and a written report within 3 working days. This includes deaths within 30 days of last drug.
   - Expected Event: Grade 4-5 regardless of attribution requires report to FER by phone/fax/e-mail within 24 hours and a written report within 3 working days.

8. If the results of an investigator or FER investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

10. Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

13.2.1 FER Responsibilities

1. Any serious or unexpected adverse event that is possibly, probably or definitely related to the study will be reported in writing to FER who will submit to Genentech and voluntarily to the FDA within 5 working days of notification of the event. Death from any cause will be reported immediately to Genentech and participating sites. The report will be distributed to all investigative sites within 15 working days of notification of the event for review by each respective IRB

2. If the results of an investigator or FER investigation show an adverse event not initially determined to be reportable is so reportable, FER will report the event following the above guidelines based on the date the determination is made.

3. FER will track all serious events and report them routinely to the Principal Investigator

for review.

4. FER will track all reports submitted to all investigative sites and ensure that all involved Institutional Review Boards (IRB) have reviewed the reports. FER will collect documentation of all IRB review.

13.3 Reporting of Serious Treatment Emergent Adverse Events (STEAEs)

All STEAEs should be recorded on a MedWatch 3500 Form and faxed to:
Study Coordination Center/Principal Investigator: Hossein Borghaei, DO
Contact Information and fax #
Holly Tuttle, RN, MSN
50 Huntingdon Pike, 2nd Floor
Rockledge, PA 19046
Fax 215-728-4784

Safety Reporting Requirements for IND Exempt Studies
For **Investigator Sponsored IND Exempt Studies**, there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

Postmarketing 15-Day "Alert Report":
FER will notify the FDA of any fatal or life-threatening adverse event that is **unexpected and assessed by the investigator to be possibly related to the study treatment**. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be submitted to the FDA (2 copies) at the following address: Central Document Room, 12229 Wilkins Avenue, Rockville, MD 20852. All Postmarketing 15-Day "Alert Reports" submitted to the FDA by FER will also be faxed to: Genentech Drug Safety

For questions related to safety reporting, contact: Genentech Drug Safety
Tel: 1-888-835-2555 Fax: (650) 225-4682 or (650) 225-5288

14. EGFR Testing

Patients with available tissue will have paraffin-preserved biopsy or surgical specimens from the primary or metastatic site utilized for detection of EGFR expression by IHC by the commercially available DakoCytomation EGFR pharmDx™ test kit. This test scores samples based on positive/negative and 1-3+ to indicate intensity of staining. Standard methodology will be applied.

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Appendix A

Study Flowchart

	Baseline [11]	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Every Cycle Till progression	Off Study[12]
Informed Consent	X[14]						
H+ P and PS & Vitals	X[1]	X[15]	X	X	X	X	X
CT(C/A)[13] (MRI if needed)	X[7]		X[5]		X	X[5]	X[9]
CT or MRI brain	X[7]						
Pathology	X[6]						
CBC, Diff and Plt.	X	X[15]	X	X	X	X	X
Comprehensive Panel	X[2]	X[15]	X	X	X	X	X
PT/PTT/INR	X	X[15,10]	X[10]	X[10]	X[10]	X	X
UA for Protein: Creatinine Ratio	X[3]		X		X		X
Toxicity Assessment	X	X[15]	X	X	X	X	X[8]
Serum β-HCG	X[4]						
FACT-L Assessment	X		X[5]		X	X[5]	X
Charlson Co-Morbidity Index	X[16]						

1. History to include documentation of prior treatments and rationale for treatment with this combination.
2. Baseline Glucose, Bun, Creatinine, Uric Acid, Total Bilirubin, Alkaline Phosphatase, LDH, Total protein, Albumin, SGOT (AST), SGPT (ALT), Calcium. All ≤ 14 days prior to enrollment.
3. Required prior to treatment with bevacizumab and then pre-treatment (D1) every other cycle. Baseline must be calculated from UA, on treatment testing can be done by dipstick.
4. For Women of childbearing potential.
5. CT scans and FACT-L Assessment will be done after every two cycles. After the sixth cycle, disease imaging assessment will be done every 12weeks.
6. For EGFR through IHC and FISH (if feasible)
7. Scans to be done within 28 days prior to enrollment
8. Follow until resolved. Patients should be seen in clinic or contacted by phone within 30 $\pm$ 3 days of discontinuation of treatment for toxicity assessment.
9. Off study evaluations should not be repeated if they were just done and documented progression. Follow up evaluations in the absence of disease progression should be performed every three months-until death
10. Repeat PT/PTT/INR every cycle if on low dose coumadin.
11. All baseline studies to be done within 14 days of registration unless otherwise indicated
12. Long term follow up for survival and disease progression should be conducted every 3 months for 2 years, then every 6 months for 2 years, the annually until death
13. PET/CT permitted, if that is what is available from initial workup, as baseline if CT component has readable measurable disease. CT will be used to follow lesions.
14. Informed consent must be obtained prior to any study related procedures. If ≥ 30 days from time consent is signed and subject is registered, subject must re-sign ICF.
15. Baseline H&P, PS, CBC, Chem, coags, UA for protein:creat ratio, VS may be used for C1D1. If used, patient must be seen by study coordinator to assess for changes in status. For subsequent cycles, Day 1 CBC, Chem & UPC ratio may be done up to 2 days prior to D1.
16. To be performed by treating MD or designee.

APPENDIX B
National Cancer Institute Common Toxicity Criteria, Version 3
Obtain from http://ctep.info.nih.gov/CTC3/ctc.htm

APPENDIX C
List of CYP3A4 Inhibitors

- From http://www.georgetown.edu/departments/pharmacology/davetab.html

The following are known inhibitors of CYP3A4:

Delaviridine	Indinavir
Nelfinavir	Ritonavir
Saquinavir	Amiodarone
Cimetidine	Ciprofloxacin
Clarithromycin	Diethyl-dithiocarbamate
Diltiazem	Erythromycin
Fluconazole	Fluvoxamine
Gestodene ++	Grapefruit juice
Itraconazole	Ketoconazole
Mifepristone	Nefazodone
Norfloxacin	Norfluoxetine
Mibefradil	Troleandomycin
Atazanavir	Indinavir
Telithromycin	Voriconazole

The following are known inducers of CYP3A4:

Rifampicin	Phenytoin
Rifabutin	Rifapentine
Carbamazepine	Phenobarbital
St. John's Wort	

APPENDIX D
ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX E
NEW YORK HEART ASSOCIATION GUIDELINES

- class I no limitation of physical activity
- class II slight limitation of physical activity
- class III marked limitation of physical activity
- class IV inability to carry out any physical activity without discomfort

APPENDIX F
Procedure for Obtaining a Urine Protein / Creatinine Ratio

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
2) Determine protein concentration (mg/dL)
3) Determine creatinine concentration (mg/dL)
4) Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)
Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

APPENDIX G
FACT-L (version 4.0)

FACT-L (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-L (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-L (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4

APPENDIX H
Charlson Co-Morbidity Index

Instructions for completing THE COMORBIDITY RECORDING SHEET:
To be completed by the treating MD at baseline.

1. Refer to the protocol for assessments to be used as a basis for data collection.
2. Complete all patient/institution information.
3. Extract all comorbidity elements you can identify and note them on the Recording Sheet. Place the elements in the most appropriate category. Be comprehensive.
4. Include past surgeries, diseases, smoking history, and functional problems, such as incontinence or constipation.
5. If a functional problem appears to be related to tumor or treatment, place **TR** after the diagnosis.
6. Include medications, and specify as much as possible the dose/frequency. The investigators may use this information to rate the severity of a disease.
7. Include all pertinent baseline laboratory values in your assessment of comorbidity.
8. Leave the scoring column blank.

Instructions for completing THE CHARLSON COMORBIDITY INDEX:

1. Complete all patient/institution information.
2. Follow the "Rules for Completing The Charlson Comorbidity Index" in this appendix.
3. Complete the Charlson Comorbidity Index by noting "yes" or "no" for each disease.

COMORBIDITY RECORDING SHEET

Name/Number:_____
Patient Initials *(Last, First)***:**_____ **Number:**_____
Name of Person Completing Sheet:_____
Phone Number:_____
Date Completed:__-___-_____

Comorbidities *(Add **TR** if related to tumor or its treatment)*	Score *(Optional)*
Heart	
Vascular	
Respiratory	
Eyes and ENT	
Upper GI	
Lower GI	
Liver and Pancreas	
Renal *(Creatinine:)*	
GU	
Musculoskeletal/Integument	
Neurological	
Endocrine/Metabolic and Breast *(Weight: Height:)*	
Psychiatric	

Medications	

APPENDIX H ***(continued)***

Rules for Completing the Charlson Comorbidity Index *(CCI)*

Adaptation: Do not count non-melanotic skin cancers or in situ cervical carcinoma.

(Charlson et al. *J Chron Dis*. 40:373-383, 1987)

Myocardial infarct	Hx of medically documented myocardial infarction
Congestive heart failure	Symptomatic CHF w/ response to specific treatment
Peripheral vascular disease	Intermittent claudication, periph. arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneuvrysm (>=6cm)
Cerebrovascular disease (except hemiplegia)	Hx of TIA, or CVA with no or minor sequellae
Dementia	chronic cognitive deficit
Chronic pulmonary disease	symptomatic dyspnea due to chronic respiratory conditions (including asthma)
Connective tissue disease	SLE, polymyositis, mixed CTD, polymyalgia rheumatica, moderate to severe RA
Ulcer disease	Patients who have required treatment for PUD
Mild liver disease	cirrhosis without PHT, chronic hepatitis
Diabetes (without complications)	diabetes with medication
Diabetes with end organ damage	retinopathy, neuropathy, nephropathy
Hemiplegia (or paraplegia)	hemiplegia or paraplegia
Moderate or severe renal disease	Creatinine >3mg% (265 umol/l), dialysis, transplantation, uremic syndrome
2nd Solid tumor (non metastatic)	Initially treated in the last 5 years *exclude non-melanomatous skin cancers and in situ cervical carcinoma*
Leukemia	CML, CLL, AML, ALL, PV
Lymphoma, MM...	NHL, Hodgkin's, Waldenström, multiple myeloma
Moderate or severe liver disease	cirrhosis with PHT +/- variceal bleeding
2nd Metastatic solid tumor	self-explaining
AIDS	AIDS and AIDS-related complex *Suggested: as defined in latest definition*

APPENDIX H ***(continued)***

Name/Number:_____
Patient Initials *(Last, First)***:**_____ **Number:**_____
Name of Person Completing Sheet:_____
Phone Number:_____
Date Completed:__-___-_____

CHARLSON COMORBIDITY INDEX *(CCI)*

Comorbidity	Present	Points
Myocardial infarct		1
Congestive heart failure		1
Peripheral vascular disease		1
Cerebrovascular disease (except hemiplegia)		1
Dementia		1
Chronic pulmonary disease		1
Connective tissue disease		1
Ulcer disease		1
Mild liver disease		1
Diabetes (without complications)		1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2

2nd Solid tumor (non metastatic)		2
Leukemia		2
Lymphoma, MM...		2
Moderate or severe liver disease		3
2nd Metastatic solid tumor		6
AIDS		6

Total points: _____

Comments: