RC1126

Academic and Community Cancer Research United (ACCRU)

A Randomized Phase II Trial of Erlotinib Alone or In Combination with Bevacizumab in Patients with Non-Small Cell Lung Cancer and Activating Epidermal Growth Factor Receptor Mutations

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Drug Availability

Drug Company Supplied: Erlotinib (Commercial supply) and Bevacizumab (Commercial supply)

√ Study contributor(s) not responsible for patient care.

Study Participants	**Date Activated**
ACCRU Membership	March 16, 2012

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Schema

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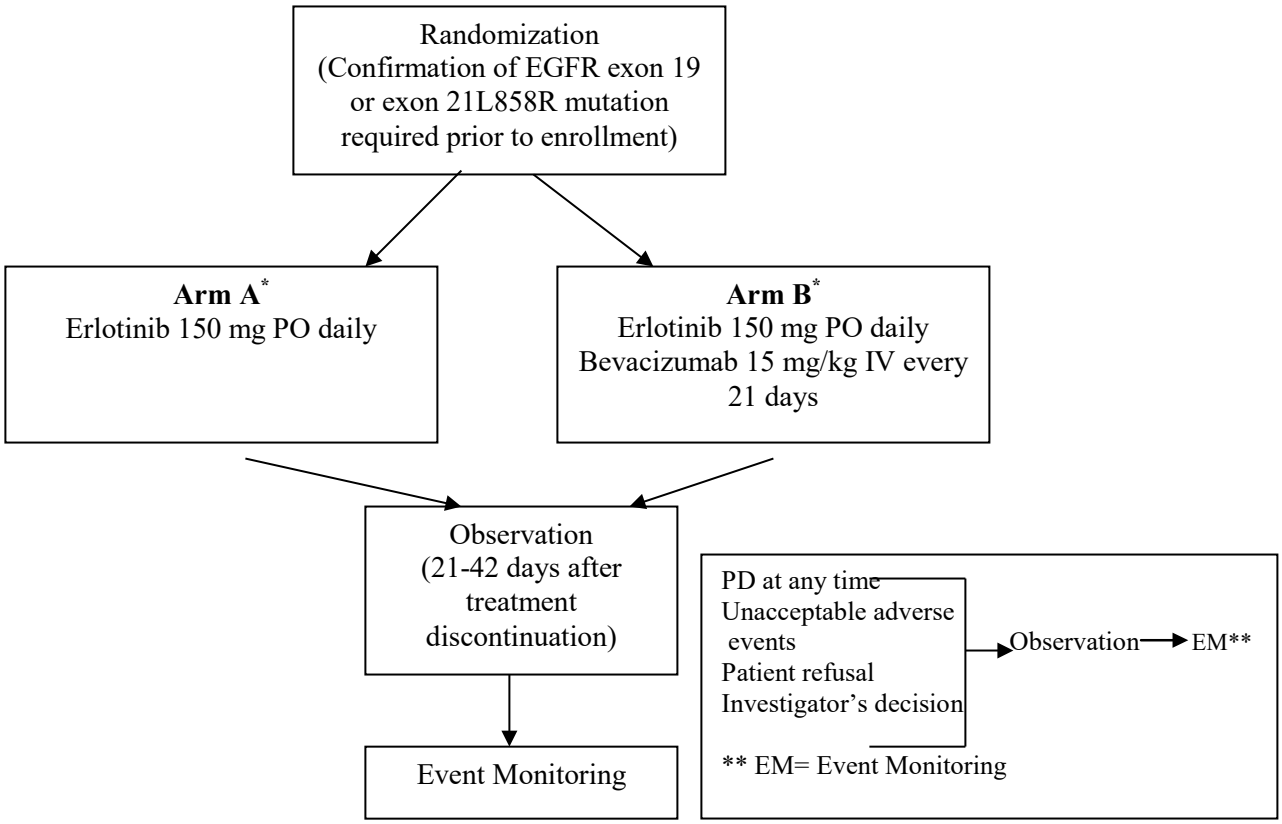
Schema

NOTE: With amendment 10, Erlotinib (Tarceva) will no longer be supplied by Genentech to participants on this study. Therefore, all patients currently taking Erlotinib will be removed from study treatment and have the option to transition to the commercial product. No further follow-up will be required by any study participants after September 1, 2019.



*Cycle Length = 21 days
Therapy will be continued until disease progression, unacceptable toxicity, or patient withdraws consent.

Generic name: Erlotinib Brand name(s): Tarceva ACCRU Abbreviation: OSI774 Availability: ACCRU Research Coordinating Center Pharmacy	Generic name: Bevacizumab Brand name(s): Avastin ACCRU Abbreviation: AVASTN Availability: ACCRU Research Coordinating Center Pharmacy

1.0 Background

Lung cancer is the leading cause of cancer mortality in the United States, and it is estimated in 2010 more patients died from lung cancer than colon, breast cancer, and prostate cancer combined.[Jemal *et al.*, 2010] Eighty-seven percent of patients with lung cancer will have non-small cell lung cancer (NSCLC), and the majority of patients will present with locally advanced or metastatic disease.[Yang *et al.*, 2005, Govindan *et al.*, 2006] Tobacco use accounts for 90% of the cases of lung cancer in men, and 75-85% of the cases in women. Approximately 10-15% of cases of lung cancer occur in patients who have never smoked in the United States.[Subramanian *et al.*, 2007] Given the prevalence of lung cancer in the United States this represents a substantial patient population. Lung cancer in never smokers appears to have a different prognosis and response to therapy.[Nordquist *et al.*, 2004, Dibble *et al.*, 2005, Tsao *et al.*, 2006] A history of a light or never smoking history is associated with a higher response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy (e.g. erlotinib or gefitinib), and this patient population has a higher prevalence of activating EGFR mutations. [Pao *et al.*, 2004, Thatcher *et al.*, 2005] Other clinical factors associated with a higher prevalence of activating EGFR mutations are adenocarcinoma histology, Asian ethnicity, and female gender.[Pao *et al.*, 2005, Thatcher *et al.*, 2005] The prevalence of these mutations in the overall patient population in Europe and the United States is estimated to be 10-15%.[Sequist *et al.*, 2007] The prevalence among patients with a history of never-smoking in Europe or the United States is estimated to be approximately 35-40%.[Sequist *et al.*, 2007, Rosell *et al.*, 2009] The specific EGFR mutations that are associated with response are deletion of exon 19, and an exon 21 L858R point mutation. Retrospective data suggest that patients with NSCLC whose tumors have the exon 19 compared to L858R mutations may have a better survival with EGFR TKI therapy. [Jackman *et al.*, 2006, Riely *et al.*, 2006]

Several single arm phase II trials have investigated the efficacy of EGFR TKI therapy in patients whose tumors have demonstrated the presence of an activating EGFR mutation. [Asahina *et al.*, 2006, Sequist *et al.*, 2008, Inoue *et al.*, 2009] A phase III non-inferiority trial with the primary end-point of PFS investigated the efficacy of single agent gefitinib in comparison to carboplatin and paclitaxel was performed in Asia. [Mok *et al.*, 2009] Patients were required to have an adenocarcinoma histology, a never or light smoking history (defined as $\leq$ 10 pack years and quit smoking $\geq$ 15 years ago), and a performance status of 0 to 2. Treatment with gefitinib demonstrated superiority in PFS compared to carboplatin and paclitaxel (HR = 0.74, 95% CI, 0.65 to 0.85; $p<0.001$). A higher response rate was observed among patients who received treatment of the gefitinib arm in comparison to the carboplatin and paclitaxel arm (43% vs. 32.2%, respectively; odds ratio (OR) 1.59 (95% CI, 1.25 to 2.01; $p<0.001$). A lower rate of common toxicity criteria (CTC) grade 3 to 4 treatment related adverse events was observed of the gefitinib arm compared to the carboplatin and paclitaxel arm (28.7% versus 61%, respectively). A statistically significant higher rate of improvement quality of life (Qol) assessment and symptom reduction was observed among patients on gefitinib arm compared to patients on carboplatin and paclitaxel arm as assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L) and Trial Outcome Index (TOI).

Of the 1217 randomized patients 437 (35.9%) had samples analyzed for activating EGFR mutations and the prevalence of mutations in this clinically enriched patient population was 60% (n=261). Of these 261 samples, 140 (53.6%) had exon 19 deletions, and 111 (42.5%) had a mutation at exon 21. In the subset of patients with evidence of an activating EGFR mutation (n=261) patients who received gefitinib experienced a statistically significant improvement in PFS in comparison to patients who received carboplatin and paclitaxel (HR=0.48, 95% CI, 0.36 to 0.64; $p<0.001$; median 9.5 vs. 6.3 months, respectively). The response rate was significantly higher among patients who received gefitinib in comparison to carboplatin and paclitaxel as well (71.2% vs. 47.3%, $p<0.001$). Conversely among patients without evidence of an activating EGFR mutation (n=176) the patients who received gefitinib experienced a statistically significant inferior PFS in comparison to patients who received carboplatin and paclitaxel (HR=2.85, 95% CI, 2.05 to 3.98; $p<0.001$). The response rate was significantly lower among patients who received gefitinib in comparison to patients who received carboplatin and paclitaxel (1.1% vs. 23.5%, OR=0.04, 95% CI, 0.01 to 0.27; p=0.001); one patient responded to the gefitinib. Not enough events have occurred to assess the secondary end-point of OS.

A phase III trial performed in Japan compared treatment with gefitinib to carboplatin and paclitaxel among patients with EGFR mutations and the absence of the resistant EGFR mutation T790M.[Maemondo *et al.*, 2010] The primary end-point was PFS, and secondary end-points were overall survival, response rate and toxicity. After a planned interim analysis the PFS was significant longer among patients in the gefitinib arm compared to the chemotherapy arm resulting in early termination of the study after 200 patients had been enrolled. Patients in the gefitinib arm experienced a significantly longer PFS (HR=0.30, 95% CI, 0.22 to 0.41; p<0.001; median 10.8 and 5.4 months, respectively), higher response rate (73.7% vs. 30.7%, p<0.001), and lower rate of grade ≥ 3 toxicity (41.2 vs. 71.7, p<0.001). The median OS observed in the gefitinib and chemotherapy treatment arms were 30.5 and 23.6 months, respectively. A second phase III trial in Japan compared gefitinib to cisplatin and docetaxel among patients with an EGFR mutation.[Mitsudomi *et al.*, 2010] The primary end-point was PFS, and enrollment to this trial was stopped after 177 patients had been enrolled when the results of other trials[Mok *et al.*, 2009, Maemondo *et al.*, 2010] had revealed a superior PFS with gefitinib among patients with an EGFR mutation were publicly presented. Patients in the gefitinib treatment arm experienced a significantly longer PFS (HR=0.489, 95% CI 0.336 to 0.710; p<0.0001; median PFS 9.2 and 6.3 months, respectively), and higher response rate (62.1% vs. 32.2%, respectively). Not enough events have occurred to assess the secondary end-point of OS.

A separate study performed in Europe screened patients for an activating EGFR mutation, and identified mutations in 16.6% of patients and among 37.7% of patients with history as having never smoked.13 In the 217 patients who received erlotinib the median PFS and OS observed was 14 months (95% CI, 11.3 to 16.7) and 27.0 months (95% CI, 22.7 to 31.3), respectively. The PFS and OS were similar in patients who received erlotinib as first and second-line therapy. However, poor progressive-free survival was associated with the presence of the L858R mutation (HR=1.92; 95% CI, 1.19 to 3.10; p=0.02) as well as OS (HR=2.98 (95% CI, 1.48 to 6.04); p=0.002), and on a multivariate analysis of OS the L858R mutation was associated with poor prognosis. A randomized phase III trial compared erlotinib to four cycles of carboplatin and gemcitabine in patients with an EGFR mutation (n=154); the primary end-point was PFS. [Zhou *et al.*, 2011] The PFS was significantly longer among patients in the erlotinib arm compared to the chemotherapy arm (HR=0.16, 95% CI, 0.10-0.26; p<0.0001; median PFS 13.1 and 4.6 months, respectively) and the overall response rate was higher as well (83% vs. 36%, p<0.0001). Patients assigned to the erlotinib compared to the chemotherapy had a significant improvement in their quality of life as assessed by the FACT-L and LCS score (p<0.0001). A second phase III trial compared erlotinib to platinum-based therapy in patients with an EGFR mutation; the primary end-point was PFS. [Rosell *et al.*, 2011] The patients assigned to the erlotinib arm compared to the chemotherapy arm experienced a significantly longer PFS (HR=0.37, 95% CI, 0.25 to 0.54; p<0.0001); median PFS of 9.7 and 5.4 months, respectively). The overall response rate in the erlotinib and chemotherapy arm was 58 and 15%, respectively.

In summary these phase III trials have demonstrated the superiority of EGFR TKI therapy in patients with evidence of activating EGFR mutation, and the inferiority of EGFR TKI therapy as initial therapy in patients who do not have evidence of an activating EGFR mutation in comparison to standard chemotherapy. The IPASS trial demonstrated that clinical criteria alone (smoking history, histology, and ethnicity) cannot be used alone to select for patients who may benefit from first-line therapy with EGFR TKI therapy. The median PFS observed with EGFR TKI therapy in patients with an activating EGFR mutation was 9.2 to 13.1 months on these trials. The current American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) guidelines recommend first-line EGFR TKI therapy for patients with an EGFR mutation.[Azzoli *et al.*, 2009, Ettinger *et al.*, 2010]

1.1 Cancer and Leukemia Group B 30406

Four phase III trials have investigated chemotherapy alone versus in combination with EGFR TKI therapy in unselected patient populations.[Giaccone *et al.*, 2004, Herbst *et al.*, 2004, Herbst *et al.*, 2005, Gatzemeier *et al.*, 2007] On a retrospective analysis of patients with a history of never smoking (n=72) who received chemotherapy in combination with erlotinib (n=28) had a superior survival to patients who received chemotherapy alone (n=44) (HR=0.49, 95% CI 0.28 to 0.85; median overall survival of 22.5 vs. 10.1 months).[Herbst *et al.*, 2005] These data led to the development of Cancer and Leukemia Group (CALGB) trial 30406, a randomized phase II trial of erlotinib alone or in combination with carboplatin and paclitaxel in patients with adenocarcinoma and a light or never smoking history.[Janne *et al.*, 2010] The primary end-point was PFS, and the trial was not designed to compare the two treatment arms. In the erlotinib alone arm (n=81) the PFS and OS observed was 6.7 months (95% CI, 4.0 to 8.3) and 24.3 months (95% CI, 18.4 to 31.3), respectively. In the chemotherapy and erlotinib arm the PFS and OS observed was 6.6 months (95% CI, 5.4 to 8.2) and 19.6 (95% CI, 14.4 to 28.7), respectively. Among patients in the erlotinib arm with an EGFR mutation (n=33) the PFS and OS observed were 15.7 months (95% CI, 8.6 to 20.4) and 31.3 months (95% CI, 23.8 to 42.8), respectively. Patients with an activating EGFR mutation (n=33) compared to EGFR wild-type (n=44) experienced a statistically significant longer PFS and OS in the erlotinib alone arm. Among patients with an activating EGFR mutation (n=33) in the erlotinib with carboplatin and paclitaxel arm the PFS and OS observed were 17.2 months (95% CI, 10.3 to not available (NA)) and 39.0 (95% CI, 38.1 to NA), respectively. In the erlotinib and chemotherapy treatment arm the patients with activating EGFR mutation (n=33) compared to the EGFR wild-type (n=54) experienced a statistically significant longer PFS and OS. Patients in the erlotinib and chemotherapy arm experienced a numerically higher rate of hematologic and non-hematologic toxicity compared to patients in the erlotinib alone arm.

1.2 Bevacizumab

In addition to the development of EGFR TKI therapy for advanced NSCLC the development of anti-angiogenesis therapy has been an area of active investigation. Two phase III trials have been performed comparing standard platinum-based therapy with and without bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), in patients with chemotherapy naïve advanced NSCLC.[Sandler *et al.*, 2006, Reck *et al.*, 2009; 2010] Eastern Oncology Group (ECOG) trial 4599, compared carboplatin and paclitaxel with and without bevacizumab, and revealed a statistically significantly superior response rate (35% vs. 15%, p<0.001) , PFS (HR=0.66, 95% CI, 0.57 to 0.77; p< 0.001; median 6.2 and 4.5 months) and OS (HR=0.79, 95% CI, 0.67 to 0.92; p=0.003) with the addition bevacizumab to platinum-based chemotherapy.[Sandler *et al.*, 2006] A second phase III trial compared cisplatin, gemcitabine, and placebo to the cisplatin and gemcitabine with bevacizumab 7.5 mg/kg or 15 mg/kg every 3 weeks with the primary end-point of PFS, and secondary end-point of OS.[Reck *et al.*, 2009; 2010] Patients in cisplatin, gemcitabine, and bevacizumab 7.5 mg/kg treatment arm compared to cisplatin, gemcitabine, and placebo arm experienced a superior response rate (34.1% vs. 20.1%, p<0.0001) and PFS (HR=0.75, 95% CI, 0.62 to 0.91; p=0.003; median PFS 6.7 and 6.1 months, respectively), but no improvement in OS (HR=093, 95% CI, 0.78 to 1.11; p=0.420; median OS 13.6 and 13.1 respectively). Patients in the cisplatin, gemcitabine, and bevacizumab 15 mg/kg compared to the cisplatin, gemcitabine, and placebo arm experienced a superior response rate (30.4% vs. 20.1%; p=-.0023), and PFS (HR=0.82, 95% CI, 0.68 to 0.98; p=0.03: median PFS 6.5 and 6.1 months, respectively), but no difference is OS (HR=1.03, 95% CI, 0.86 to 1.23; p=0.761, median OS 13.4 and 13.1 months, respectively).

A single arm phase II trial revealed promising activity of the combination of erlotinib and bevacizumab in patients who had progressed after previous chemotherapy.[Herbst *et al.*, 2011] A phase III trial compared erlotinib alone or in combination with bevacizumab in patients who had progressed on chemotherapy (n=650) with the primary end-point of overall survival. The overall survival was not different between the erlotinib and bevacizumab in comparison to erlotinib and placebo (HR=0.97, 955 CI, 0.80-1.18; p=0.7583; median OS 9.3 and 9.2 months, respectively).Patients who received erlotinib and bevacizumab in comparison to patients who received erlotinib experienced a statistically significant higher response (13% vs. 6%, p=0.006), and improved PFS (HR=0.62, 95% CI, 0.52 to 0.75; p<0.0001, median PFS 3.4 and 1.7 months. respectively). In the subset of patients with a history of never smoking (n=67) the combination therapy demonstrated a statistically significantly superior PFS (HR=0.39 (95% CI, 020 to 0.74: p=0.0295) and OS (HR=0.44, 95% CI, 0.21 to 0.94; p=0.0295). Of the 636 patients enrolled tumor samples were available on 477 patients. In a subset analysis of patients with activating EGFR mutation (n=30) the combination of erlotinib and bevacizumab (n=12) demonstrated a numerically superior PFS in comparison to erlotinib and placebo (n=18); HR=0.52, 95% CI, 0.19 to 1.38); median PFS of 17.1 months vs. 9.7 months).[Herbst *et al.*, 2009] The overall survival observed in the erlotinib and bevacizumab was numerically superior to erlotinib and placebo (HR=0.44, 95% CI, 0.11 to 1.67; median survival time not reached and 20.2 months, respectively).[Herbst *et al.*, 2011].

A phase II trial investigated erlotinib compared to erlotinib and bevacizumab in patients with an EGFR exon 19 deletion or exon 21 L858R mutations [Seto et al 2014]. The primary end-point was PFS by independent radiological review and 154 patients were enrolled. Patients assigned to the erlotinib and bevacizumab compared to the erlotinib alone arm experienced a statistically significant difference in PFS (HR of 0.54, 95% CI, 0.36 to 0.79; p=0.0015: median 16.0 and 9.7 months). In a subset analysis, patients with exon 19 deletion mutations (n=80) who received erlotinib and bevacizumab compared to erlotinib alone experienced statistically significant longer PFS (HR of 0.41, 95% CI, 0.24 to 0.72; p=0.0011; median PFS of 18.0 and 10.3 months, respectively). In a subset analysis patients exon 21 L858R mutations (n=72) who received erlotinib and bevacizumab compared to erlotinib experienced a numerically longer PFS (HR of 0.67, 95% CI< 0.38 to 1.18; p=0.01653; median PFS of 13.9 and 7.1 months, respectively). The most common grade ≥ 3 adverse events in the erlotinib/bevacizumab and erlotinib arms were rash (25% vs. 19%), hypertension (60% vs. 10%), and proteinuria (8% vs.0%).

At the time the trial was written treatment anti-coagulation was a relative contraindication for treatment with bevacizumab. Since the initiation of the trial additional data has revealed that the treatment of patients on anticoagulation do not experience an increased risk of severe bleeding events. [Leighl et al 2011] Importantly, no episodes of severe pulmonary hemorrhage were observed in patients on therapeutic anticoagulation. Several recently completed trials of bevacizumab in advanced NSCLC have allowed patients on therapeutic anticoagulation to be enrolled or remain on trial if full dose anticoagulation is required. [Reck et al 2009] Additional safety data is available from the phase IV Safety of Avastin in Lung cancer study (SAiL) of 2,212 patients which did not reveal an increased risk of bleeding events with concomitant use of bevacizumab and anticoagulation. [Crino et al 2010]. The current Eastern Cooperative Oncology Group trial which is investigating bevacizumab in combination with carboplatin and paclitaxel allows for full dose anti-coagulation (NCT01107626). Thus, we are amending the trial to allow full dose anti-coagulation.

The management of patients with brain metastases receiving bevacizumab has changed since the time the protocol was written. The original protocol was based on a phase II trial the eligibility criteria were based on bevacizumab starting 4 weeks after completion of radiation therapy to brain metastases.[Socinski *et al.*, 2009] A prospective phase II trial demonstrated the safety of using bevacizumab with first-line chemotherapy or second-line erlotinib in patients with asymptomatic untreated brain metastases.[Besse *et al.*, 2013] In addition to the data from treatment of patients with NSCLC and brain metastases there are data several phase III trials have investigated the role of bevacizumab in the treatment of glioblastoma. A phase III trial initiated bevacizumab week 4 of a 6 week course of radiotherapy in combination with temozolomide.[Gilbert *et al.*, 2014] A second phase III trial in glioblastoma initiated bevacizumab concurrently with temozolomide and radiation, and continued bevacizumab after completion of radiation therapy.[Chinot *et al.*, 2014] In order to be consistent with literature and other trials investigating bevacizumab (e.g. Eastern Cooperative Oncology Group 5508, NCT01107626) we have amended the trial so that patients with treated brain metastases would be eligible if ≥ 2 weeks since completion of any radiotherapy and radiation therapy for treatment of brain metastases.

1.3 Epidermal Growth Factor Tyrosine Kinase Inhibitor Resistance

Despite the significant effects of EGFR TKIs in EGFR mutant NSCLC, all patients eventually develop resistance to single agent EGFR TKI treatment. This typically occurs between 8-14 months from initiating treatment. Two common mechanisms of acquired resistance to gefitinib and erlotinib have been identified; secondary mutations in EGFR itself (EGFR T790M) or amplification of the MET oncogene.[Kobayashi *et al.*, 2005, Pao *et al.*, 2005, Shih *et al.*, 2005, Kosaka *et al.*, 2006, Bean *et al.*, 2007, Engelman *et al.*, 2007] In addition, a recent study suggested that EGFR T790M may pre-exist in EGFR mutant caners prior to gefitinib or erlotinib treatment [Maheswaran *et al.*, 2008]. Those patients in whom a pre-treatment EGFR T790M was detected (n=10) had a shorter time to disease progression than patients without detectable EGFR T790M (N=16), 7.7 months and 16.5 months ($p<0.001$).[Maheswaran *et al.*, 2008] The detection of the T790M can be difficult because of allelic dilution due to the fact that the EGFR gene is amplified but only a few copies of T790M allele are needed to confer resistance which may obscure results with conventional sequencing methods.[Janne, 2008]

As resistance occurs in all patients, it is critical to identify effective treatments for EGFR mutant NSCLC patients that may overcome acquired resistance or prevent or delay the emergence of acquired resistance. Unfortunately, repeat biopsies to detect the mechanisms of EGFR TKI resistance frequently are not feasible and/or associated with risk to the patient which may be difficult to justify given the poor prognosis associated with advanced stage NSCLC. The issue is further complicated by the fact that many biopsies provide insufficient material for molecular analysis.

The tumor specimens from this trial will provide a valuable resource in which to perform correlative studies on EGFR mutations. These include the ability to correlate plasma detected EGFR mutations with tumor EGFR mutations and to study the pre-existence of erlotinib resistance mechanisms. This trial can prospectively assess whether patients with pre-existing EGFR T790M mutations have a shorter TTP with erlotinib (or erlotinib/bevacizumab) treatment. If so, such findings would have significant future therapeutic implications including the use of second generation irreversible EGFR inhibitors as initial therapy

1.4 Epidermal Growth Factor Receptor mutation testing

The testing for the EGFR mutation will be performed prior to enrollment on this clinical trial. The results of the IPASS and other phase III trials have led to EGFR mutational testing becoming more prevalent, particularly in patient populations clinically likely to have a high prevalence of activating EGFR mutations. In recent months an increasing percentage of patients who present for a second opinion have previously undergone EGFR mutational analysis prior to their appointment indicating that this practice has already gained acceptance among community oncologists. For enrollment in the trial the EGFR mutation testing must be performed at Clinical Laboratory Improvement Amendments (CLIA) certified lab; either institutional or through a commercial laboratory (e.g. Genzyme, Response Genetics, etc). The laboratory reports from the commercial laboratories report the specific mutations detected, including the exon 19 and exon 21 L858R point mutations.

2.0 Goals

2.1 Primary

2.11 To determine the progression-free survival of erlotinib and bevacizumab versus that of erlotinib alone for the purpose of deciding if the combination arm is worth pursuing in a phase III trial.

2.2 Secondary

2.21 To investigate the overall survival of erlotinib and bevacizumab versus erlotinib alone.

2.22 To investigate the response rate of erlotinib and bevacizumab versus erlotinib alone.

2.23 To investigate the progression-free survival in patients with exon deletion 19 or exon 21 L858R point mutations.

2.24 To investigate the toxicity of erlotinib and bevacizumab versus erlotinib alone using CTCAE version 4.0.

2.3 Correlative Research

2.31 To correlate EGFR mutations detected in plasma DNA with those detected in tumor DNA.

2.32 To estimate the prevalence of EGFR T790M resistance mutations from pre-treatment tumor biopsies using more sensitive mutation detection methods.

2.33 To investigate progression free survival of EGFR mutant NSCLC patients with and without concurrent EGFR T790M detected from pre-treatment tumor specimen using allele specific quantitative PCR.

2.34 To prospectively evaluate the predictive value of plasma VEGF-A levels on progression free survival in patients treated with erlotinib alone or in combination with bevacizumab.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histologic documentation of primary lung carcinoma, non-squamous histology with activating epidermal growth factor receptor (defined as deletion 19 or exon 21 L858R mutation). **Note:** EGFR mutation testing must be performed at a Clinical Laboratory Improvement Amendments (CLIA) certified lab; either institutional or through a commercial laboratory (e.g. Genzyme, Response Genetics, etc). The laboratory report from the commercial laboratories report the specific mutations detected, and the method of detecting the exon 19 and exon 21 L858R point mutations must be available.

3.13 Stage IV disease according to the 7th Edition of the American Joint Committee on Cancer staging system [Goldstraw *et al.*, 2007]

3.14 Measureable disease as defined in Section 11.0 [Eisenhauer *et al.*, 2009].

3.15 Life expectancy of ≥12 months.

3.16 ECOG Performance Status (PS) 0 or 1 (See Appendix III).

3.17 The following laboratory values obtained ≤ 14 days prior to randomization.

- ANC ≥ 1, 500 / mm^3
- Platelet count, ≥ 100,000 / mm^3
- Hemoglobin ≥ 9.0 g / dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- SGOT (AST) and SGPT (ALT) ≤2.5 x ULN in patients without liver or bone metastases; < 5 x ULN in patients with liver or bone metastases.
- Cockcroft-Gault calculated creatinine clearance of ≥ 45 ml/min* or creatinine ≤1.5 x ULN
- Urine dipstick proteinuria <2+ or urine protein/creatinine (UPC) ratio ≤1.0

Note: Patients discovered to have ≥2 + proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.

* Cockcroft-Gault formula:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

3.18 Negative pregnancy test done ≤7 days prior to randomization, for women of childbearing potential only.

3.19a Provide informed written consent.

3.19b Willing to return to ACCRU enrolling institution for follow-up.

3.19c Willing to provide tissue and blood samples for correlative research purposes (see Sections 6.0, 14.0 and 17.0)

3.2 Exclusion Criteria

3.21 Mixed, non-small cell and small cell tumors or mixed adenosquamous carcinomas with a predominant squamous component.

3.22 Prior chemotherapy or treatment for metastatic non-small cell lung cancer.

3.23 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.24 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.25 Immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be HIV positive, per MD discretion.

3.26 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations, or any other medical condition that would limit compliance with study requirements.

3.27 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.28 Other active malignancy ≤ 3 years prior to randomization. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment (i.e. hormonal therapy) for their cancer.

3.29a History of myocardial infarction or other evidence of arterial thrombotic disease (angina), symptomatic congestive heart failure (New York Heart Association ≥ grade 2), unstable angina pectoris, or cardiac arrhythmia . Note: Allowed only if patient has no evidence of active disease for at least 6 months prior to randomization.

3.29b History of cerebral vascular accident (CVA) or transient ischemic attack (TIA) ≤6 months prior to randomization.

3.29c History of bleeding diathesis or coagulopathy.

3.29d Inadequately controlled hypertension (systolic blood pressure of >150 mmHg or diastolic pressure >100 mmHg on anti-hypertensive medications). Note: History of hypertensive crisis or hypertensive encephalopathy not allowed.

3.29e Current or recent (≤10 days prior to randomization) use of aspirin (>325 mg/day), clopidogrel (> 75 mg/day), or prasugrel (> 10 mg/day).

3.29f Serious non-healing wound, ulcer, bone fracture, or have undergone a major surgical procedure, open biopsy, or significant traumatic injury ≤ 28 days or core biopsy ≤ 7 days prior to randomization.

3.29g History of abdominal fistula, gastrointestinal perforation, or intraabdominal abscess ≤6 months prior to randomization.

3.29h Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

3.29i History of hemoptysis ≥grade 2 (defined as bright red blood of at least 2.5 mL) ≤ 3 months prior to randomization.

3.29j Known CNS disease, except for treated brain metastasis. Note: 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 ≤3 months prior to randomization will be excluded. Note: Craniotomy or intracranial biopsy site must be adequately healed, free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization. Study treatment should be initiated > 28 days following the last surgical procedure (including biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity).

3.29k Significant vascular disease (e.g. aortic aneurysm surgical repair or recent peripheral arterial thrombosis) ≤6 months prior to randomization.

3.29l Radiotherapy to any site for any reason ≤ 14 days prior to randomization.

3.29m Receiving any medications or substances that are **strong or moderate inhibitors** of CYP3A4.

Use of the following strong or moderate inhibitors is prohibited ≤ 7 days prior to randomization:

Strong Inhibitors of CYP3A4 > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance
Indinavir (Crixivan®) Nelfinavir (Viracept®) Atazanavir (Reyataz®) Ritonavir (Norvir®) Clarithromycin (Biaxin®, Biaxin XL®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®) Nefazodone (Serzone®) Saquinivir (Fortovase®, Invirase®) Telithromycin (Ketek®)
Moderate Inhibitors of CYP3A4 > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance
Aprepitant (Emend®) Erythromycin (Erythrocin®, E.E.S. ®, Ery-Tab®, Eryc®, EryPed®, PCE® Fluconazole (Diflucan®) Grapefruit juice Verapamil (Calan®, Calan SR®, Covera-HS®, Isoptin SR®, Verelan®, Verelan PM®) Diltiazem (Cardizem®, Cardizem CD®, Cardizem LA®, Cardizem SR®, Cartia XT™, Dilacor XR®, Diltia XT®, Taztia XT™, Tiazac®)

3.29n Receiving any medications or substances that are **inducers** of CYP3A4.

Use of the following inducers are prohibited ≤ 7 days prior to randomization:

Inducers of CYP3A4
Efavirenz (Sustiva®) Nevirapine (Viramune®) Carbamazepine (Carbatrol®, Epitol®, Equetro™, Tegretol®, Tegretol-XR®) Modafinil (Provigil®) Phenobarbital (Luminal®) Phenytoin (Dilantin®, Phenytek®) Pioglitazone (Actos®) Rifabutin (Mycobutin®) Rifampin (Rifadin®) St. John's wort

4.0 Test Schedule

Tests and Procedures	Active Monitoring Phase				
	≤14 days prior to randomization	Prior to each cycle (≤ 7 days)	Re-staging every 2 cycles for 18 months from randomization, then every 4 cycles until disease progression	At PD, withdrawal, or removal[12]	Observation[4,12] (21-42 days after treatment discontinuation)
History and exam including weight, blood pressure, smoking history	X	X[5, 8]			X
ECOG PS	X	X		X	X
Adverse event assessment	X	X[9]			X
Urine dipstick proteinuria or urine protein creatinine ratio	X	X			
Hematology: CBC/ differential, PT/INR[6], PTT[6]	X	X[7]			
Chemistry: SGOT (AST), SGPT (ALT), alk phos, T. bili, creatinine, calcium, phosphorus, glucose, Na, K	X	X[6,7]			
Tumor measurement (see Section 11.0)	X[11]		X[3]	X	X
MRI or CT scan of brain[10]	X				
Pregnancy test	X[1]				
Mandatory blood sample (see Section 14.0)[2, R]	X		X	X	
Mandatory tissue sample (see Section 17.3)[R]	X				

1. For women of childbearing potential only. Must be done ≤ 7 days prior to randomization.
2. See Section 14.241. Kits are required for this collection. Research blood sample to be drawn prior to treatment.
3. Patients should undergo imaging for disease progression every 2 cycles for the initial 18 months, then after 18 months every 4 cycles until disease progression. Submit relevant radiographic images as a digital image (via CD) with a viewing tool free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s) of tumor response at baseline and tumor response and/or progression. Submit CD's to the A[redacted]
4. All patients (including those who have left the study because of progressive disease, unacceptable toxicity, patient refusal, investigator's decision to remove patient, etc) must have a toxicity check at this time point.
5. Hypertensive medication should be initiated or increased per routine practice.
6. PT/INR, PTT, glucose, calcium, phosphorus, Na, and K at baseline and then only as clinically indicated.
7. Only SGOT (AST), SGPT (ALT), alk phos, T. bili, and CBC/differential checked on Day 1 of each cycle.
8. Smoking history collected only at baseline.
9. Prior to subsequent cycle.
10. MRI is the preferred test for imaging for brain metastases, CT scan with contrast is acceptable for patients who are unable or intolerant of undergoing MRI of the brain. Patients must have either MRI or CT scan prior to randomization. MRI and CT scans should be done < 28 days prior to randomization.
11. Tumor measurements should be done < 28 days prior to randomization.
12. Patients who discontinue study therapy prior to disease progression should be followed until disease progression. The schedule of follow-up imaging is at the discretion of physician, but an interval of 6 to 12 weeks is recommended.

R Research funded (see Section 19.0)

5.0 Stratification Factors

5.1 Gender: Male vs. female.

5.2 Mutation type: Exon 19 vs. Exon 21 L858R.

6.0 Registration/Randomization Procedures

6.1 Randomization Procedures

6.11 To register a patient, access the ACCRU web page at [redacted] click on "Training Page" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available by using the Help button. Prior to initiation of protocol study intervention, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.0, 14.0 and 17.0).

6.13 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.14 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.15 At the time of randomization, the following will be recorded:

- Patient has/has not given permission to store and use his/her blood for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her blood for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission to store and use his/her tissue for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her tissue for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.

6.16 Treatment cannot begin prior to randomization and must begin ≤14 days after randomization.

6.17 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.18 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.19a Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.19b Study drug is available on site.

6.19c Blood draw kit is available on site.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock and Simon 1975. [Pocock *et al.*, 1975]

- Arm A: Erlotinib 150 mg daily
- Arm B: Erlotinib 150 mg daily and bevacizumab 15 mg/kg every 21 days

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

Patients will be randomized between arm A (erlotinib alone) and arm B (erlotinib and bevacizumab), and will continue treatment until disease progression according to response evaluation criteria for solid tumors (RECIST) 1.1[38]or unacceptable toxicity. One cycle will considered 21 days on both treatment arms. Patients will be assessed for response using the radiological test used at baseline every 2 cycles for the initial 18 months, and then every 4 cycles until disease progression from time to randomization.

Arm	Agent	Dose Level	Route	Day	ReRx
A	Erlotinib	150 mg	PO	Daily	Every 21 days
B	Erlotinib	150 mg	PO	Daily	
	Bevacizumab*	15 mg/kg	IV	1	

* The first dose will be administered over 90 (± 10) minutes. If well-tolerated, the second dose may be administered over 60 (± 10) minutes. Again, if well-tolerated, subsequent doses may be administered over 30 (± 10) minutes. If the patient is pre-medicated for infusion reaction, maintain previous infusion rate for first pre-medicated infusion. If well-tolerated with pre-medication, the subsequent infusion time may then be decreased by 30 minutes, as long as the subject continues to be pre-medicated. If the patient experiences infusion associated adverse events with the 60-minute infusion, all subsequent infusions should be given over 90 minutes. Similarly, if a patient experiences infusion associated adverse events with the 30-minute infusion, all subsequent doses should be given over 60 minutes.

7.2 Erlotinib only: Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.3 For this protocol, the patient must return to an ACCRU institution for evaluation at least every 21 days (+/- 7 days).

7.4 Treatment by a local medical doctor (LMD) is not allowed.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose. If patients discontinue either agent, they will go to observation and event monitoring.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Bevacizumab: This section applied to adverse events associated with bevacizumab. For Adverse events associated with erlotinib, please refer to Section 8.2.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
BASED ON OBSERVED ADVERSE EVENT		
CARDIAC DISORDERS	Left Ventricular Systolic Dysfunction	
	Grades 1-2	No dose modifications
	Grade 3	Omit bevacizumab until resolution to Grade ≤1.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Myocardial Infarction	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
GASTROINTESTINAL DISORDERS	Rectal Perforation	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
	Small Intestinal Perforation	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
	Colonic Perforation	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
	Gastric Perforation	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
	Colonic Obstruction	
	Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
	Grade 2	Omit bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
	Grade 3-4	Omit bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
	Small Intestinal Obstruction	
	Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
	Grade 2	Omit bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
	Grade 3-4	Omit bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
	Anal Hemorrhage	

	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Colonic Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Duodenal Hemorrhage	
	Grade 1 or 2	No dose modifications.

	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Rectal Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Oral Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.

	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Lower Gastrointestinal Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Jejunal Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Intra-abdominal Hemorrhage	
	Grade 1 or 2	No dose modifications.

	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Ileal Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Gastric Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.

	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Esophageal Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Upper Gastrointestinal Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Retroperitoneal Hemorrhage	
	Grade 1 or 2	No dose modifications.

	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
HEPATOBILIARY DISORDERS	Hepatic Hemorrhage	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Wound dehiscence	
	Any Grade (requiring medical or surgical therapy)	Discontinue bevacizumab, go to observation and event monitoring.
NERVOUS SYSTEM DISORDERS	Leukoencephalopathy (confirmed by MRI)	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
	Ischemia cerebrovascular	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
	Intracranial hemorrhage	

	Grade 1	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
	Grade ≥2	Discontinue bevacizumab, go to observation and event monitoring.
RENAL AND URINARY DISORDERS	Hematuria	
	Grade 1 or 2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Proteinuria	
	Grade 1 defined as any of the following: 1. Urine dipstick 1 2. Urine protein level 0.15-1.0g/24 hrs on 24 hour urine collection 3.Urine protein creatinine ratio ≤ 0.15-1.0)***	No dose modifications.

	Grade 2 defined as any of the following: 1.Urine dipstick 2+ 2.Urine protein level >1-3.4g/24 hrs on 24 hour urine collection 3.Urine protein creatinine ratio > 1.0 to 3.4)***	1. Omit bevacizumab for ≥2 grams/24 hrs or urine protein creatinine ratio of ≥ 2 and resume when proteinuria is <2 grams/24 hr or urine protein/creatinine ratio < 2.0 2. For urine <2 grams/24 hrs or urine protein creatinine ratio < 2 may proceed with bevacizumab treatment 3. For 2+ dipstick obtain 24 hour urine or urine protein/creatinine ratio prior to treatment with bevacizumab
	Grade 3 defined as any of the following: 1. Urine dipstick 3+ or 4+ 2. Urine protein level >3.5g/24 hrs on 24 hour urine collection 3. Urine protein creatinine > 3.5)***	1. Omit bevacizumab for ≥2 grams/24 hrs or urine protein creatinine ratio of ≥2 and resume when proteinuria is <2 grams/24 hrs or urine protein/creatinine ratio < 2.0 2. For grade 3+ or 4+ omit bevacizumab and obtain a 24 hour urine or urine protein creatinine ratio. Omit bevacizumab for ≥2 grams/24 hrs or urine protein creatinine ratio of ≥2 and resume when proteinuria is <2 grams/24 hrs or urine protein/creatinine ratio < 2.0 3. For urine <2 grams/24 hrs or urine protein creatinine ratio < 2 may proceed with bevacizumab treatment
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	Vaginal Hemorrhage	
	Grade 1-2	No dose modifications.
	Grade 3	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • 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 from receiving bevacizumab, go to observation and event monitoring.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Tracheal fistula	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
	Fistula	
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.
	Bronchopulmonary hemorrhage	
	Grade 1-2	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
	Grade ≥2	Discontinue bevacizumab, go to observation and event monitoring.
	Pleural hemorrhage	
	Grade 1	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab omitted until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence
	Grade ≥2	Discontinue bevacizumab, go to observation and event monitoring
VASCULAR DISORDERS	Hypertension	
	Grades 1-2	No dose modifications.
	Grade 3	If not controlled to 150/100 mmHg with medication, discontinue bevacizumab, go to observation and event monitoring.
	Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab, go to observation and event monitoring.
	Peripheral Ischemia	
	Any Grade	Discontinue bevacizumab, go to observation and event monitoring.
	Thromboembolic Event	
	Grade 1-2	No dose modifications.

	Grade 3-4	Discontinue bevacizumab, go to observation and event monitoring
OTHER UNSPECIFIED ADVERSE EVENTS ASSOCIATED WITH BEVACIZUMAB	Grade 3	Omit until resolved to ≤Grade 1.
	Grade 4	Discontinue bevacizumab, go to observation and event monitoring.

**If dose is omitted more than 2 cycles, patient should go off study and go to observation and event monitoring. If patient discontinues bevacizumab, they will come off study (i.e. patients cannot continue on single agent erlotinib and remain on study). Patients will go to observation and event monitoring.

*** Urine protein creatinine ratio can be reported in several formats. The mg/g approximates the protein excretion in mg/24 hours.

8.2 Erlotinib: This section applies to adverse events associated with erlotinib. For adverse events associated with bevacizumab, please refer to Section 8.1.

Dose modification table

Dose level	Erlotinib dose
0	150 mg daily
-1	100 mg daily
-2	50 mg daily

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
BASED ON OBSERVED ADVERSE EVENT		
GASTROINTESTINAL DISORDERS	Diarrhea	
	Grades 1-2	See Section 9.8 for symptom-related control. Continue erlotinib at the same dose level and institute treatment for diarrhea. If Grade 2 persists over 48-72 hours despite optimal medical management, decrease erlotinib by 1 dose level.
	Grade 3	See Section 9.8 for symptom-related control. Omit erlotinib and institute treatment for diarrhea. Once diarrhea resolves to ≤Grade 2, resume with one dose level reduction. If erlotinib is omitted for >21 days, discontinue erlotinib, go to observation and event monitoring.
	Grade 4	Discontinue erlotinib, go to observation and event monitoring.
	Small Intestinal Perforation	
	Any Grade	Discontinue erlotinib, go to observation and event monitoring.
	Colonic Perforation	
	Any Grade	Discontinue erlotinib, go to observation and event monitoring.
	Gastric Perforation	
	Any Grade	Discontinue erlotinib, go to observation and event monitoring.
	Esophageal Perforation	
	Any Grade	Discontinue erlotinib, go to observation and event monitoring.
EYE DISORDERS	Keratitis (corneal inflammation /corneal ulceration)	
	Grade 1	Continue treatment. See Section 9.8.
	Grade 2	Omit in cases of persistent Grade 2 keratitis (>14 days) while on therapy. See Section 9.8.
	Grade 3	Discontinue, see Section 9.8. Go to observation and event monitoring
	Eye Pain	
	Grade 3	Omit until Grade ≤2 then ↓ dose by the dose levels in the above table.
	Grade 4	Discontinue erlotinib, go to observation and event monitoring. See Section 9.8.
INVESTIGATIONS	Aspartate aminotransferase increased	
	≥Grade 3 (i.e. >5x ULN)	Omit until grade ≤2 then ↓ dose by the following dose levels according to current treatment dose (150 mg → 100 mg →50 mg).

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
BASED ON OBSERVED ADVERSE EVENT		
	Blood Bilirubin Increased	
	≥Grade 3 (i.e. >3x ULN)	Omit until grade 0-2 then ↓ dose by the following dose levels according to current treatment dose (150 mg → 100 mg →50 mg).
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash Acneiform	
	Grades 1-2	Continue at the same dose level and institute treatment of rash (See Section 9.8). If Grade 2 rash persists and is intolerable, dose reduction according to the dose modification table above should be considered, and continuing erlotinib at the reduced dose is an option. Alternatively, treatment interruption until rash is tolerable and dose reduction according to the dose modification is an option. Maximum interval of erlotinib interruption is 21 days. Once patient requires a dose reduction, dose re-escalation is not allowed.
	Grade 3	See Section 9.8 for symptom-related control. Continue erlotinib at the current dose. If skin rash is intolerable, dose reduction according to the dose modification table above and continuing erlotinib at the reduced dose is an option. The preferred option is a treatment interruption until rash is tolerable and dose reduction according to the dose modification. Maximum interval of erlotinib interruption is 21 days. Once patient requires a dose reduction, dose re-escalation is not allowed.
	Grade 4	Discontinue erlotinib, go to observation and event monitoring.
OTHER UNSPECIFIED ADVERSE EVENTS ASSOCIATED WITH ERLOTINIB	Grade 2	For symptomatic patients, the dose may be omit until recovery to grade 0-1, initiate at the same dose.
	≥Grade 3	Omit drugs until grade ≤2, then ↓ dose by the following dose levels according to current treatment dose (150 mg → 100 mg →50 mg).

**Patients who require discontinuation of the erlotinib for greater than 21 consecutive days will go off treatment and go to observation and event monitoring.

**Erlotinib should not be restarted in those suspected of having drug-related interstitial lung disease (ILD).

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for all subsequent cycles.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on treatment. These dose reductions must be clearly recorded in reported clinical data.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 24, No 19 (July 1), 2006: pp. 3187-3205.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Hypertension is a known and potentially serious adverse event associated with bevacizumab treatment. An increase in blood pressure of >20 mmHg (systolic) and 10 mmHg (diastolic) should be reported to the treating physician immediately (see Section 8.0 for hypertension management and dose reduction guidelines).

9.6 Anti-platelet therapy (e.g., ≤ 325 mg/day aspirin) should be considered for the treatment of patients at high risk of developing an arterial thromboembolic event unless contraindicated and may be continued in patients receiving it at time of entry. Patients developing bleeding on study should be evaluated for possible bevacizumab discontinuation as described in the protocol.

9.7 Patients who experience infusion-associated temperature elevations to ≥ 38.5°C (101.3°F) or other infusion-associated symptoms may be treated symptomatically with acetaminophen, diphenhydramine, meperidine, or other medications as clinically indicated.

9.8 Management of erlotinib-associated adverse events

9.81 Rash: Patients should be informed that skin toxicity is to be expected during treatment with erlotinib. Rash was the most commonly reported adverse event considered related to erlotinib therapy in phase III trials. Rash typically develops within 8 to 10 days of initiation of treatment but may appear within 1 to 113 days. Although the rash is commonly referred to as "acneiform", it is not acne, but rather a papulopustular reaction, and should not be treated as acne. Patients are recommended to wear sun screen protection, hat, long sleeves to avoid sun as it can exacerbate skin rash.

Redness and/or a warm sensation of the skin can be an initial indicator in the development of erlotinib-related rash. Tender skin and inflammatory pustules and papules begin to appear on the face, head, and upper torso as the rash develops, and the rash is typically accompanied by pruritis, dry skin, and erythema. Most incidences of rash are intermittent and mild to moderate in severity. When accurately managed, rash and other erlotinib-related skin toxicities generally do not interfere with a patient's treatment; however, a small proportion of patients may experience a severe rash that could lead to significant physical and/or cosmetic discomfort and may require discontinuation of therapy at the patient's request.

In addition to rash, other erlotinib-related skin toxicities include dry, itchy, or flaky skin (especially on the scalp); increased growth of facial hair (including eyelashes/brows); small skin fissures on the fingertips; brittle and/or loose fingernails; sores around the eyes, corners of the mouth, or inside the nose; easily bruised skin; dry, itchy eyes; inflammation around the nails (especially thumbs and big toes) sometimes accompanied by pain; and decreased hair growth and/or hair loss on the legs, arm, and scalp.

Prophylactic treatment of the skin may prevent or reduce skin toxicity. Patients should avoid soap as it is drying and use bath oil with tepid water when bathing. The patient should be encouraged to use an alcohol-free, emollient cream applied twice a day to the entire body as soon as the patient starts therapy with erlotinib. Creams and ointments are recommended because they have a greater ability to retain moisture than lotions. Examples of suitable emollient creams include: Neutrogena® Norwegian formula, SARNA® Ultra, Vanicream™, Aveeno® (fragrance-free formulation), and Eucerin® cream. Other over-the-counter aqueous creams or emulsifying ointments may also provide symptomatic benefit. Lotions should be avoided because they often contain alcohol, which will dry the skin. Patients should also be encouraged to use a titanium dioxide or zinc oxide-based sunscreen product applied to sun-exposed areas twice per day.

Patients who develop skin toxicity and are symptomatic should be treated with topical therapy such as hydrocortisone cream or clindamycin gel. If needed, oral minocycline or oral doxycycline may be combined with the topical therapy. A topical immodulating cream such as Elidel could also be considered. For more severe rash, oral corticosteroids may be beneficial. Patients who fail to respond to these measures may have the dose of erlotinib interrupted or reduced. See Appendix II for more information on skin toxicity management.

Minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly.

9.82 Diarrhea: previous trials have shown that the frequency of severity of diarrhea rarely hindered administration of erlotinib and could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at the first onset, followed by 2 mg every 2-4 hours (4 mg every four hours can be given at night) until diarrhea free for 12 hours.

9.83 Keratitis: Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks. Any symptoms of keratitis (corneal inflammation/corneal ulceration) should prompt an ophthalmologic evaluation as soon as possible

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires submission of a Med Watch report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Section 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is listed in Section 15.0 of the protocol as **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements: (Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/adverse events form]; see footnote 1):

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expediently reported.
Gastrointestinal Disorders	Diarrhea	Grade 3
Renal and Urinary Disorders	Proteinuria	Grade 3
Skin and Subcutaneous Tissue Disorders	Rash Acneiform	Grade 3
Vascular Disorders	Hypertension	Grade 3

1. These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.311 **Persistent or Significant Disabilities/Incapacities**
Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.312 **Death**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**
  - Death attributable to a CTCAE term.
  - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
  - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
  - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
  - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.313 **Secondary Malignancy**

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.314 **Second Malignancy**

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.31 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
2. If FDA Form 3500A (MedWatch) was completed, Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form need not be completed.
3. Submit form to the FDA, MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, by fax at 1-800-332-0178 or online at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

   Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the ACCRU SAE Coordinator.

   Non-MCCC Institutions: Provide copies by fax [redacted] to the ACCRU SAE Coordinator.

   The ACCRU SAE Coordinator will forward a copy of the expedited reports using the Genentech Fax Coversheet to:

   - Genentech Drug Safety at [redacted]

4. **Pregnancy -** Any reports of pregnancy following the start of administration with the Erlotinib & Bevacizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the Erlotinib or Bevacizumab should be reported as an SAE.

EVENT TYPE	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Notification form: Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form to MCCRC within 5 working days[2]

10.5 Other Required Reporting

10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Hepatobiliary Disorders	Hepatic Hemorrhage	X	X
Gastrointestinal Disorders	Diarrhea	# stools per day	X
	Anal Hemorrhage	X	X
	Colonic Hemorrhage	X	X
	Duodenal Hemorrhage	X	X
	Rectal Hemorrhage	X	X
	Oral Hemorrhage	X	X
	Lower Gastrointestinal Hemorrhage	X	X
	Jejunal Hemorrhage	X	X
	Intra-Abdominal Hemorrhage	X	X
	Ileal Hemorrhage	X	X
	Gastric Hemorrhage	X	X
	Esophageal Hemorrhage	X	X
	Upper Gastrointestinal Hemorrhage	X	X
	Retroperitoneal Hemorrhage	X	X
Renal and Urinary Disorders	Hematuria	X	X
	Proteinuria	X	X
Reproductive System and Breast Disorders	Vaginal Hemorrhage	X	X
Respiratory, Thoracic and Mediastinal Disorders	Bronchopulmonary Hemorrhage	X	X
	Pleural Hemorrhage	X	X
Skin and Subcutaneous Tissue Disorders	Rash Acneiform	X	X
Vascular Disorders	Hypertension	X	X

10.51 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.511 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.512 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.513 Grade 5 AEs (Deaths)

10.5131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.52 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.53 All non-serious adverse events originating from the study will be forwarded by ACCRU in a quarterly report to Genentech.

10.54 Study Close-Out- Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all Clinical Study Reports (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study.

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (Eisenhauer et al 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 6 weeks for 18 months then every 3 months until disease progression, unacceptable toxicity, or withdraw of consent.

Patients who discontinue study therapy prior to disease progression should be followed until disease progression. The schedule of follow-up imaging is at the discretion of physician, but an interval of 6 to 12 weeks is recommended.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

     i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
     ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
     iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

Complete Response (CR): All of the following must be true:

a. Disappearance of all target lesions.

b. Each target lymph node must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR): All of the following must be true:

a. Disappearance of all non-target lesions.

b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Smoking Status: Never smoker (less than 100 cigarettes in a lifetime) vs. light smoker (under 10 pack years and quit at least 15 years ago) vs. former smoker (quit greater than 1 year ago and less than 15 years or greater than 10 pack years) vs. current smoker.

12.2 Weight loss ≤3 months: <10% vs. ≥10%.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase. Complete the Event Monitoring Form at the time of PD. Patient will then be observed 21-42 days following discontinuation of treatment and will then go to event monitoring (see Section 18.0).

13.3 Patients will continue treatment until PD, unacceptable toxicity, investigator's decision remove patient from the study, patient refusal to continue, or alternate treatment. Treatment will then be discontinued. Patients will be observed 21-42 days following discontinuation of treatment and will then go to event monitoring (see Section 18.0).

13.4 Patients who go off protocol treatment for reasons other than PD will go to observation per Section 4.0 (day 21-42 days after treatment discontinuation), and then to the event-monitoring phase per Section 18.0.

13.5 Patients who develop PD in the CNS only should receive appropriate treatment for brain metastases and should be considered as having progressive disease.

13.6 Patients who develop non-CNS PD at any time should go to event monitoring. Complete the Event Monitoring Form at the time of PD. Patient will then be observed 21-42 days following discontinuation of treatment and will then go to event monitoring (see Section 18.0). These patients should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

13.7 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 (see Section 8.0).

13.8 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.9a A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.9b A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol.

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission

14.11 Summary Table of Body Fluid Biospecimens for This Protocol

Type of biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for specimen submission**
Blood/blood products (no additive whole blood)	Mandatory	Multiple draws (see Section 14.24 for schedule)	Defined translational studies (Section 14.4)	Section 14.2

14.2 Blood/Blood Products Handling

14.21 **Kits are required for this study.**

14.211 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to Biospecimen Accessioning and Processing (BAP) Receiving or the BAP Shared Resource.

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **ACCRU will <u>not</u> cover the cost for rush delivery of kits.**

14.22 All Samples must be collected **Monday – Friday**.

14.23 Label specimen tube(s) with protocol number, ACCRU patient ID number, and time and date blood is drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions and table below.

14.241 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Baseline	Every 2 cycles until 18 months from randomization	Every 4 cycles after 18 months until progression	At Progression, withdrawal, removal	Additional processing required at site after blood draw?	Storage /shipping conditions[1]
Mandatory	None (red)	10 ml (1)	Serum	X	X	X	X	Yes	Freeze/dry ice
Mandatory	Purple	10 ml (1)	Plasma EGFR mutation	X	X	X	X	Yes	Freeze/dry ice
Mandatory	Purple	10 ml (1)	Platelet Poor Plasma VEGF-A	X				Yes	Freeze/dry ice

1. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions).

14.25 Shipping

14.251 Verify ALL sections of the Research Blood Submission Form (see Forms Packet), BAP Requisition Form (provided in kit) and specimen collection labels are completed and filled in correctly. Enter information from the Blood Specimen Submission Form into the remote data entry system ≤1 day after specimen collection (see Forms Packet).

14.252 Specimens should be shipped the same day they are drawn unless drawn on a Friday. Then specimens should be stored frozen at -80◦C and shipped on the following Monday or Tuesday if Monday is a Federal Holiday.

14.253 Ship all serum and plasma via Priority Overnight service on dry ice.

14.254 Ship specimens via Priority Overnight service, **Monday – Thursday ONLY,** to BAP Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

14.255 BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label which replaces the need for a paper air bill. Shipping costs will be covered by ACCRU if the shipping box is used for shipping specimens to BAP Freezer.

14.256 BAP Freezer will receive the samples and immediately forward specimens to the ACCRU Research Coordinating Center BAP Shared Resource, Hilton SL-21, Attention: BAP Supervisor.

14.257 BAP Shared Resource will store specimens according to internal instructions.

14.3 Other Body Fluids Handling: None

14.4 Study Methodology and Storage Information

14.41 Blood/blood product samples will be collected for the following research

Plasma EGFR detection: There has been great interest in developing non-invasive methods for EGFR genotyping. This would provide a means of non-invasively evaluating whether a patient's tumor harbors an EGFR mutation if such information cannot be obtained from their diagnostic tumor biopsy. In addition such a method would have the ability to query any changes in EGFR mutations over time and in response to treatment. Most studies have found a concordance of ~70% with the tumor EGFR mutation.[Bai *et al.*, 2009, Kuang *et al.*, 2009, Rosell *et al.*, 2009] However, very few if any studies have performed such analyses prospectively and from treatment naïve advanced NSCLC patients that are undergoing treatment with EGFR inhibitors. Furthermore, the ability to detect mutations non-invasively will likely increase over time with the advent of new and novel technology. As patients need to have a known EGFR mutation at study entry, the current trial provides an ideal study in which to query the correlation of plasma and tumor EGFR mutations. The correlation with the EGFR activating mutation will be performed from the baseline (pre-treatment specimen) as all patients will be treatment naïve.

EGFR T790M: EGFR T790M is the common mechanism of drug resistance to erlotinib and is detected in up to 60% of EGFR mutant NSCLC patients that develop acquired resistance to EGFR kinase inhibitors including erlotinib.[Kobayashi *et al.*, 2005, Pao *et al.*, 2005, Oxnard *et al.*, 2011] In addition to being a drug resistance mutation, this mutation is associated with a unique biology. Prior studies have demonstrated that patients that develop this mechanism of drug resistance appear to have more indolent disease and a better overall survival.[Oxnard *et al.*, 2011] The evolution of this mutation during the course of erlotinib therapy has not been prospectively assessed from patients undergoing therapy. It will be interesting to determine at which point during the course of a patient's treatment can EGFR T790M be detected from plasma DNA and the relationship to clinical progression as defined by RECIST criteria. EGFR T790M will be assayed from plasma DNA at baseline and during each radiographic assessment and at the time of progression.

Plasma VEGF-A levels: Despite multiple efforts no biomarker has emerged that can predict the efficacy of bevacizumab. The only potential exception is pre-bevacizumab treatment plasma VEGF-A levels. Plasma VEGF-A level will be evaluated from pre-treatment plasma levels in both arms of the study and correlated with outcome. The goal is to prospectively validate the significance of plasma VEGF-A levels in patients treated with erlotinib alone or in combination with bevacizumab.

14.411 A portion of the serum/plasma will initially be analyzed for the presence of EGFR mutation and VEGF-1 in Dr. Pasi Janne's laboratory, Lowe Center for Thoracic Oncology, Dana Farber Cancer Institute, 450 Brookline Ave, HIM223, Boston, MA 02215 using standard laboratory protocols. According to patient consent information (see Section 6.15), remaining serum/plasma will be stored frozen at -70ºC by BAP, until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.412 As part of ongoing ACCRU research, we will collect serum/plasma/platelet poor plasma for future research studies, according to patient consent information (see Section 6.15), on molecular determinants of efficacy and tolerability. Samples will be stored frozen at -70ºC by BAP until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval.

14.5 Return of Genetic Testing Research Results

No genetic specimens will be collected from non-solid tissue (body fluid) biospecimens for this study. If future genetic testing is being requested for stored specimens, patient reconsent is required.

15.0 Drug Information

Investigator brochures: Investigator brochures for both agents are available on the ACCRU web site under study RC1126.

15.1 Bevacizumab (Avastin®)

15.11 **Background**: Bevacizumab is classified as an Anti-VEGF Monoclonal Antibody and a Vascular Endothelial Growth Factor (VEGF) Inhibitor. Bevacizumab is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

15.12 **Formulation**: Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and excipient/chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is > 95%.

Bevacizumab is supplied in 100 mg (4 mL) and 400 mg (16 mL) glass vials, each with a concentration of 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.

15.13 **Preparation and storage**: Bevacizumab vials should be stored in a refrigerator at 2°C-8°C. Keep vial in the outer carton due to light sensitivity. **DO NOT FREEZE. DO NOT SHAKE.**

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. **Do not administer or mix with dextrose solution.** From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/mL. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

15.14 **Administration:** Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion. Do not initiate bevacizumab for 28 days following major surgery and until surgical wound is fully healed.

Refer to Section 7 for protocol-specific administration instructions. Guidelines recommended by the manufacturer are included for reference.

First infusion: Administer infusion over 90 minutes. Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

15.15 **Pharmacokinetic information**:
Distribution: V_d: 3.28 L
Half-life elimination: 3-4 weeks
Clearance: 0.22 L/day. A low serum albumin and high tumor burden increase clearance by 30% and 7% respectively. Clearance increases with increasing body weight, and is 15% slower in women than men.
Time to steady state: 100 days

15.16 **Potential Drug Interactions**:
No clnically relevant pharmacokinetic interaction of co-administered chemotherapy on bevacizumab pharmacokinetics has been observed based on the results of a population PK analysis. There was neither statistical significance nor clinically relevant difference in clearance of bevacizumab in patients receiving bevacizumab monotherapy compared with patients receiving bevacizumab in combincation with Interferon alpha 2a or other chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

No clinically relevant interactions of bevazizumab was observed on the pharmacokinetics of co-administered interferon alpha 2a, erlotinib (and its active metabolite OSI-420), or the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of bevacizumab and sunitinib malate: In two clinical studies of metastatic renal cell carcinoma, microangiopathic hemolytic anemia (MAHA) was reported in 7 of 19 patients treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination. MAHA is a hemolytic disorder which can present with red cell fragmentation, anemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate.

15.17 **Known potential adverse events:** Consult the investigator's brochure and package insert for the most current and complete information. U.S. Boxed Warnings report that severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurs up to 5-fold more frequently in patients receiving bevacizumab products. Do not administer bevacizumab products to patients with a recent history of hemoptysis. Discontinue in patients who develop grade 3 to 4 hemorrhage. Percentages reported as Monotherapy and as part of combination chemotherapy regimens.

Very Common (≥ 1/10)
Infections and infestations: paronychia
Blood and lymphatic system disorders: febrile neutropenia, leucopenia, neutropenia, thrombocytopenia
Metabolism and nutrition disorders: anorexia, hypomagnesemia, hyponatremia
Nervous system disorders: peripheral sensory neuropathy, dysgeusia, headache, dysarthria
Eye disorders: eye disorder, increased lacrimation
Vascular disorders: hypertension
Respiratory, thoracic and mediastinal disorders: dyspnea, epistaxis, rhinitis, cough
Gastrointestinal disorders: diarrhea, nausea, vomiting, abdominal pain, constipation, stomatitis, rectal hemorrhage
Endocrine disorders: ovarian failure
Skin and subcutaneous tissue disorders: exfoliative dermatitis, dry skin, skin discoloration
Musculoskeletal, connective tissue, and bone disorders: arthralgia
Renal and urinary disorders: proteinuria
General disorders and administration site conditions: asthenia, fatigue, pyrexia, pain, mucosal inflammation
Investigations: weight decreased

Common (≥ 1/100 to < 1/10)
Infections and infestations: sepsis, abscess, cellulitis, infection
Blood and lymphatic system disorders: anemia, lymphopenia
Metabolism and nutrition disorders: dehydration
Cardiac disorders: cardiac failure congestive, supraventricular tachycardia
Vascular disorders: arterial thromboembolism, deep vein thrombosis,

hemorrhage
Respiratory, thoracic and mediastinal disorders: pulmonary embolism, hypoxia
Gastrointestinal disorders: intestinal perforation, ileus, intestinal obstruction, recto-vaginal fistula, gastrointestinal disorder, proctalgia
Skin and subcutaneous tissue disorders: palmar-plantar erythrodysesthesia syndrome
Musculoskeletal, connective tissue, and bone disorders: muscular weakness, myalgia, arthralgia, back pain
Renal and urinary disorders: urinary tract infection
General disorders and administration site conditions: lethargy
Reproductive system and breast: pelvic pain

Rare (≥ 1/10,000 to < 1/1,000)
Infections and infestations: necrotizing fasciitis
Nervous system disorders: posterior reversible encephalopathy syndrome

15.18 **Drug procurement:**
Investigational bevacizumab is provided free of charge to patients by Genentech. Each participating ACCRU membership will order a starter supply of bevacizumab from the appropriate distribution source. Fax the appropriate ACCRU Clinical Drug Order/Return Form to:

ACCRU Site	Distribution Source	Clinical Drug Order / Return Form
• Duke University Medical Center • University of North Carolina at Chapel Hill	Biologics, Inc. Attn. Clinical Research Services FAX: [redacted]	[redacted] (Located in protocol-specific Forms folder)
All other ACCRU sites	Medical Oncology Pharmacist Mayo Clinic [redacted]	[redacted] (Located in Non-protocol Specific Forms)

Each participating ACCRU membership will be responsible for monitoring the supply of bevacizumab and will use the appropriate ACCRU Clinical Drug Order/Return Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 Nursing guidelines:

15.191 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact MD. Have emergency equipment nearby and be

prepared to administer emergency treatment as ordered by MD.

15.192 Monitor urine dipstick or UPC as required by the test schedule.

15.193 Evaluate IV site regularly for signs of infiltration.

15.194 Bleeding in the absence of thrombocytopenia is a dose limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.

15.195 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.

15.196 Patient may experience Grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.

15.197 Monitor for skin rash, instruct patient to report to MD.

15.198 Monitor blood pressure. Administer antihypertensives as ordered by MD.

15.199a Monitor for signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), or myocardial infarction (MI) including new or worsening angina. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or shortness of breath to MD immediately.

15.199b Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.

15.199c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.

15.199d Patients receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained. For patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.

15.199e A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.

15.199f Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the MD.

15.199g Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important.

Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

15.199h Warn female patients of the possibility of ovarian failure and subsequent infertility. Vaginal hemorrhage is also possible. Instruct patients to report any heavy or unusual vaginal bleeding to health care team.

15.199i Warn female patients of the risk of rectovaginal fistula.

15.199j Agent may cause increased cardiotoxic effects of anthracyclines as well as toxic effects of irinotecan, sorafenib, and sunitinib. Patients who are on dual therapy with these agents should be monitored closely.

15.2 Erlotinib (OSI-774, Tarceva®)

15.21 **Background**: Epidermal growth factor receptor (EGFR) is expressed on the cell surface of both normal and cancer cells. In some tumor cells signaling through this receptor plays a role in tumor cell survival and proliferation irrespective of EGFR mutation status. Erlotinib reversibly inhibits the kinase activity of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor and thereby inhibiting further downstream signaling. Erlotinib binding affinity for EGFR exon 19 deletion or exon 21 L858R mutations is higher than its affinity for the wild type receptor. Erlotinib inhibition of other tyrosine kinase receptors has not been fully characterized.

15.22 **Formulation**: Erlotinib is currently formulated as conventional, immediate-release tablets in 25 mg, 100 mg, and 150 mg strengths. The tablets are film-coated, round, white, and bi-convex. The tablets contain lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, hypromellose, hydroxypropyl cellulose, titanium dioxide, and magnesium stearate as inactive ingredients. The film coating includes Opadry® White. Erlotinib tablets are supplied for clinical trials in either bottles or blister packs.

15.23 **Preparation and storage**: Erlotinib tablets should be stored at 25° C (77°F), with excursions permitted to 15°-30° C (59°-86°F).

15.24 **Administration:** Erlotinib should be taken orally once daily in the morning with water at least one hour before or two hours after the ingestion of food. Missed doses should not be made up. Avoid grapefruit and grapefruit juice while taking erlotinib. Patients should report any change in smoking status while taking erlotinib.

15.25 **Pharmacokinetic information**:

a) Absorption – The bioavailability of erlotinib following a single oral Food may increase bioavailability.
b) Distribution – Erlotinib is highly protein bound (92 to 95%) in humans.
c) Metabolism – Erlotinib is metabolized in humans in the liver by the hepatic cytochromes (primarily CYP3A4 and CYP3A5, and to a lesser extent CYP1A2), and the pulmonary isoform CYP1A1.
d) Excretion – Erlotinib and its metabolites are excreted predominately via the feces (> 90%), with a small amount recovered in urine.

15.26 **Potential Drug Interactions:**

A potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound (92% to 95%) or that are potent CYP3A4

inhibitors/inducers. Potent inducers of CYP3A4 activity (eg. rifampicin) increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations, while potent CYP3A4 inhibitors (eg, ketoconazole) result in increased exposure to erlotinib. It has also been shown that co-administration of erlotinib with proton pump inhibitors (e.g., omeprazole) decreases the bioavailability of erlotinib and hence the exposure to erlotinib and its metabolites. Co-administration of drugs reducing gastric acid production with erlotinib should be avoided where possible. If patients need to be treated with such drugs, then an H2-receptor antagonist such as ranitidine should be considered and used in a staggered manner. Erlotinib must be taken at least 2 hours before or 10 hours after the H2-receptor antagonist dosing. Erlotinib exposure was moderately increased when coadministered with ciprofloxacin, a CYP3A4 and CYP1A2 inhibitor.

The combination of erlotinib and a statin may increase the potial for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

Cigarette smoking (a moderate CYP1A2 inducer) has been shown to reduce erlotinib exposure by 50% to 60% (Studies OSI-774-103 and OSI-774-107). Smokers should be advised to stop smoking. Concomitant use of Tarceva with moderate CYP1A2 inducers should be avoided.
Interaction with coumarin-derived anticoagulants, including warfarin, leading to increased INR and bleeding events, which in some cases were fatal, have been reported in patients receiving erlotinib. Patients taking coumarin-derived anticoagulants should be monitored regulatrly for any changes in prothrombin time or INR.

15.27 **Known potential toxicities**:
Adverse Drug Reactions to be Considered Expected in Erlotinib-treated Patients are the following:
Eye Disorders: Keratitis, ulcerative keratitis, corneal perforation, dry eye, uveitis, growth of eyelashes, and conjunctivitis.
Gastrointestinal Disorders: Abdominal pain, gastrointestinal hemorrhage, gastrointestinal perforation, stomatitis, diarrhea, vomiting, nausea, flatulence, and dyspepsia.
General Disorders and Administration Site Conditions: Fatigue, chills, and pyrexia.
Hepatobiliary Disorders: Hepatitis, hepatic function abnormal, and hepatic failure.
Infections and Infestations: Paronychia, sepsis, cellulitis, folliculitis, pneumonia, and infection.
Injury, Poisoning and Procedural Complications: Radiation pneumonitis.
Investigations: Weight decreased
Metabolism and Nutrition Disorders: Decreased appetite, hypokalemia, and electrolyte imbalance.
Miscellaneous: Hair injury or hair color changes.
Nervous System Disorders: Peripheral neuropathy and headache.
Psychiatric Disorders: Depression
Renal and Urinary Disorders: Renal failure
Respiratory, Thoracic and Mediastinal Disorders: Acute interstitial pneumonitis, cough, lung infiltration, dyspnea, acute respiratory distress syndrome, epistaxis, alveolitis, interstitial lung disease, pneumonitis, obliterative bronchiolitis, pulmonary fibrosis, and alveolitis allergic.
Skin and Subcutaneous Tissue Disorders: Acne, Stevens-Johnson syndrome, rash pustular/rash maculo-papular, toxic epidermal necrolysis, dermatitis acneiform, dermatitis bullous, dry skin, skin hyperpigmentation, skin exfoliation, hirsutism, pruritus, onychoclasis, rash, nail disorder, rash erythematous, alopecia, and skin fissures.

For a complete list of reported erlotinib risks, please see the Consent Form, or the current version of the Investigator's Brochure.

15.28 **Drug procurement:** Genentech will supply erlotinib to the ACCRU Research Coordinating Center pharmacy. Each participating ACCRU membership will order a starter supply of erlotinib from the appropriate distribution source. Fax the appropriate ACCRU Clinical Drug Order/Return Form to:

ACCRU Site	Distribution Source	Clinical Drug Order / Return Form
• Duke University Medical Center • University of North Carolina at Chapel Hill	Biologics, Inc. Attn. Clinical Research Services [redacted]	[redacted] (Located in protocol-specific Forms folder)
All other ACCRU sites	Medical Oncology Pharmacist Mayo Clinic [redacted]	[redacted] (Located in Non-protocol Specific Forms)

Each participating ACCRU membership will be responsible for monitoring the supply of erlotinib and will use the appropriate ACCRU Clinical Drug Order/Return Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29 **Nursing Guidelines:**

15.291 Erlotinib should be taken orally once daily in the morning with water at least one hour before or two hours after food. Missed doses should not be made up.

15.292 Advise patient of possible rash, pruritus, scaling and peeling of skin. Dose reduction may be necessary. Advise patient to cover skin while in the sun, to wear sunscreen, and to moisturize skin daily. Instruct patient to report the above symptoms immediately to health care team for initiation of treatment. See Section 9.9 for treatment recommendations. Rarely Steven's Johnson Syndrome and toxic epidermal necrolysis are reported. Instruct patient to report any oral lesions and or fever immediately.

15.293 Administer antidiarrheals as indicated. Loperamide has been helpful. See Section 9.0 for treatment recommendations.

15.294 Caution patients against doubling up on missed doses. If the patient vomits after taking the tablets, the dose may be replaced ONLY if the tablets can actually be seen and counted in the emesis.

15.295 If patient complains of a dry mouth, advise the use of sugar free candies, ice chips, increasing fluid intake, or they may try Xero-Lube, an artificial saliva.

15.296 If patient complains of dry eyes, suggest artificial tears. If patient normally wears contact lenses, advise against their use. Additionally patients should report any dry eyes, eye pain, or visual changes to the study team.

15.297 Work with the patient that is experiencing weakness and fatigue. Advise frequent rest periods. Instruct patient in energy-saving lifestyle.

15.298 Patients should report any change in smoking status to the study team.

15.299a Although the causal agent is unknown, severe pneumonitis has been diagnosed in patients receiving erlotinib. Therefore the physician should be alerted if any patients develop new onset or worsening dyspnea, cough, and/or fever. The patient should be thoroughly evaluated for possible interstitial pneumonitis.

15.299b Nausea and vomiting are common. Premedicate with antiemetics and evaluate for their effectiveness.

15.299c Stomatitis may occur. Encourage proper oral care.

15.299d Instruct patient that they cannot eat grapefruit or drink grapefruit juice while on erlotinib.

15.299e Instruct patient that if they smoke they should refrain from smoking while on erlotinib as smoking is known to induce CYP1A1 and CYP1A2 and has been shown to reduce erlotinib exposure by 50 to 60%.

15.299f Monitor LFT's. Instruct patients to report any jaundice or dark colored urine to the study team.

16.0 Statistical Considerations and Methodology

16.1 Study Design

The goal of this randomized phase II trial is to compare the efficacy of erlotinib / bevacizumab (arm B) to erlotinib alone (arm A) in untreated advanced non-small cell lung cancer patients who have activating EGFR mutations, for the purpose of screening whether the combination regimen (arm B) is worthy of further investigation. Since this phase II trial is not a confirmatory study to compare survival benefits between the two treatment regimens, we use a slightly inflated Type I error to calculate sample size. The primary endpoint is the progression free survival (PFS), which is the time from the date of randomization of eligible patients with activating EGFR mutations to the date of disease progression or death of any cause, whichever comes first.

For untreated advanced NSCLC patients, the prevalence rate for EGFR mutants are about 15%. Patients meeting eligibility criteria will be screened for EGFR mutation; a total of 112 eligible patients with EGFR mutations will be randomized with 1:1 allocation to arm A and arm B. Randomization will be done using the Pocock and Simon dynamic allocation procedure with stratification on gender (male vs. female), and mutation type (exon 19 deletion vs. exon 21 L858R).

As of Addendum 5, the study size was amended to randomize 86 eligible patients with 1:1 allocation to Arm A and Arm B.

16.2 Sample Size, Accrual Time and Study Duration

A total of 118 patients with EGFR mutants are expected to register to the study. Taking 5% these patients early withdraw before randomization, a total of 112 EGFR patients will be randomized. At a randomization rate of 2 patients per months, it will take about 4.7 years to reach accrual target. All patients will be followed to the time of final analysis, approximately 12 months after the last enrollment.

According to current prospective first line trials of EGFR TKI therapy in patients with evidence of an activating EGFR mutation, the median PFS for erlotinib only is approximately 13 months.[Rosell *et al.*, 2009] Investigators look for a 5.6-month increase (43%) in median PFS, or a median PFS of 18.6 months for erlotinib/bevacizumab. The following assumptions are made while determining the statistical power: (i) the median PFS is 13 months for patients on erlotinib only (arm A) and 18.6 months for erlotinib/bevacizumab (arm B), a 43% increase in median PFS and a hazard ratio $\lambda_B/\lambda_A = 0.70$ under constant hazards; (ii) 112 eligible patients (56 per arm) with EGFR mutations will be randomized with 1:1 allocation; (iii) an accrual period of 56 months (4.7 years); and (iv) an additional follow-up of 12 months after the enrollment of the last patient. Using a stratified log rank test at a one-sided significance level of 0.20, the study has approximately 80% power to reject the null hypothesis $\lambda_B/\lambda_A = 1$ and accept the alternative hypothesis $\lambda_B/\lambda_A < 1$ when the true $\lambda_B/\lambda_A = 0.70$. At the time of analysis, or approximately 5.7 years after the first enrollment, a total of 88 events (47 on arm A and 41 on arm B) are anticipated under the alternative hypothesis.

As of March 6, 2015, a total of 38 patients have been randomized. Based on the positive results from Seto et al (2014), we amended the sample size of this trial by reducing the hazard ratio λ_B/λ_A from 0.70 in the original design to 0.667. In particular, we assume that (i) the median PFS is 10 months for patients on erlotinib only (arm A) and 15 months for erlotinib/bevacizumab (arm B), a 60% increase in median PFS and a hazard ratio $\lambda_B/\lambda_A = 0.667$ under constant hazards; (ii) 86 eligible patients (43 per arm) with EGFR mutations will be randomized with 1:1 allocation; (iii) an accrual period of 43 months (3.6 years); and (iv) an additional follow-up of 12 months after the enrollment of the last patient. Using a stratified log rank test at a one-sided significance level of 0.20, the study has approximately 81% power to reject the null hypothesis $\lambda_B/\lambda_A = 1$ and accept the alternative hypothesis $\lambda_B/\lambda_A < 1$ when the true $\lambda_B/\lambda_A = 0.667$. At the time of analysis, or approximately 4.6 years after the first enrollment, a total of 69 events (37 on arm A and 32 on arm B) are anticipated under the alternative hypothesis.

The time of analysis (after first patient enrolled), at which 69 events occur, is estimated to be 53 months (95% CI=47-55 months). The analysis will be conducted when 69 events have occurred. The power of the study design under this timing criterion is approximately 79%.

16.3 Primary Endpoint and Analysis

The primary endpoint is progression-free survival (PFS). The primary hypothesis is that erlotinib / bevacizumab (arm B) will improve PFS relative to erlotinib alone (arm A) in untreated advanced non-small cell lung cancer patients who have activating EGFR mutations. The relative efficacy in term of PFS in favor of erlotinib / bevacizumab warrants further investigator of the experimental regimen in a future phase III trial. The primary analysis will include all randomized patients, regardless of the treatment received. Progression free survival (PFS) is defined as the time from randomization to disease progression and death of any cause, whichever comes first. The primary analysis will be carried out after 88 events have been observed. The Kaplan and Meier product limit estimator[Kaplan *et al.*, 1958] will be used to graphically describe progression free survival for patients randomized to each treatment arm. From these product limit estimates, median survival and 12-month progression free survival rate and their 95% confidence intervals by treatment arms will be derived. Comparisons of PFS between arms will be conducted using a stratified log rank test.[Mantel, 1966]. The association of baseline prognostic factors with PFS, such as performance status, gender and mutation type,

will be evaluated one by one in univariate analysis. Cox proportional hazards model[Cox, 1972] will be used to estimate the adjusted hazard ratios and their 95% confidence intervals of arm B relative arm A with adjusting for significant baseline prognostic factors. Interactions between treatment and the significant prognostic factors will be tested in a Cox proportional hazards model with treatment, prognostic factors and the interaction terms as possible predictors. Hazard ratio for treatment effect will be estimated for each subgroup of patients that has significant interaction with treatment. The robustness of treatment effects in different patient subgroups will examined in Forest plots.

16.4 Interim Analysis Design for Primary Endpoint

No interim analysis is planned for the primary endpoint.

16.5 Supplementary Analysis Plans

To address secondary objective 2.21, we will carry out the same set of analyses described in section 16.3 for overall survival (OS), which is defined as the time from randomization to death of any causes.

To address secondary objective 2.22, we will estimate the proportion of patients who respond (completely or partially) to each treatment as well as their 95% confidence intervals. Response rates will be tested using Fisher's exact test and multivariately using a logistic regression model with performance status, gender and genetic mutation type and other significant prognostic factors.[Cox *et al.*, 1989]

To address secondary objective 2.23, we will estimate the progression free survival of patients with different mutation types (exon deletion 19 vs. exon 21 L858R), and test survival difference of these subgroups using Cox proportional hazard model after adjusting for treatment effect. The robustness of treatment effect in different subgroups will be examined in a Forest plot.

To address secondary objective 2.24, we will tabulate the types and the frequency of treatment-related adverse events for erlotinib and bevacizumab and erlotinib using CTCAE version 4.0.

To address correlative objective 2.31, we will evaluate the agreement of EGFR mutations detected in plasma DNA with those detected in tumor DNA. Since only those patients with tumor EGFR mutation will have plasma EGFR mutation determined, we are able to estimate the true positive rate (sensitivity) but not the false positive rate (1-specificity).

To address correlative objective 2.32, we will estimate the prevalence of EGFR T790M resistance mutations from pre-treatment tumor.

To address correlative objective 2.33, we will investigate the effect of EGFR T790M on progression-free survival using similar methods for 2.23.

To address correlative objective 2.34, we will use time-dependent ROC curve and AUC to evaluate the predictive value of plasma VEGF-A levels on progression free survival in patients treated with erlotinib alone or erlotinib/bevacizumab.

16.6 Adverse Event Stopping Rule

Overall, if 5 or more of the first 20 patients in the erlotinib and bevacizumab arm (or 25% of all patients after 20 are accrued) experience grade 4/5 non-hematologic adverse events (excluding diarrhea and rash) that are probably, possibly, or definitely related to study treatment, OR if the rate of treatment-related deaths within the first 60 days exceeds 4 or more in either arm among the first 20 patients (or >20% after the first 20 patients in either arm) at any time, accrual to the

study will be suspended to allow for investigation. After consideration by the study team (study chair[s], statistician, etc.) and the primary IRB, a decision will be made as to whether accrual can be resumed, potentially with modifications to entry criteria and/or study conduct. In addition, all toxicity patterns will be monitored by an independent Mayo Clinic Data Safety Monitoring Board on a bi-annual basis.

16.7 Accrual Monitoring Stopping Rule

The accrual will be monitored closely by the study team. If the trial is not terminated for adverse events or other unexpected reasons, accrual will continue until the target accrual is met, approximately 4.7 years after the first enrollment.

As of Addendum 5, the sample size is reduced and the accrual time is shortened to approximately 3.6 years.

16.8 Study Monitoring (reports)

This study will be monitored by the Mayo Clinic Data Safety Monitoring Board (DSMB). Reports containing patient characteristics, toxicity, and administrative information will be provided to the DSMB every six months, with the first report due at the first reporting period after study initiation.

16.9a Missing Data

Missing and incomplete data will be identified through a review of the tables and listings of summarizing available data. Identified missing and incomplete data will be resolved by inquiries from data coordinators. In general, unresolvable missing data will be treated as missing in all analyses. The secondary endpoints, such as response rate, patients without an assessment of disease response will be treated as non-responder.

16.9b Primary Endpoint Completion Time Estimation

It will take additional l2 months of follow-up after the last enrollment to have the primary endpoint completion, or equivalently about 5.7 years after the first enrollment.

As of Addendum 5, the sample size is reduced and the time for primary endpoint completion is now estimated 4.6 years after the first enrollment.

The time of analysis (after first patient enrolled), at which 69 events occur, is estimated to be 53 months (95% CI=47-55 months). The analysis will be conducted after 69 events have occurred.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for biospecimen submission
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E (**OR** 15 5-micron unstained slides with 2 corresponding H&E)	Mandatory	≤30 days after registration	Correlative Studies Assessment of pre-treatment EGFR T790M	Section 17.3
Formalin-fixed paraffin-embedded (FFPE) tissue blocks (**OR** 5 10-micron unstained slides)	Mandatory	≤30 days after registration	Correlative studies Assessment of tumor status performed centrally (Section 17.5)	Section 17.3

Note: If an institution is not able to provide the tissue, it does not cause the patient to be ineligible; however, the collection of these tissues is strongly recommended.

17.2 Diagnostic Slides from Original Tissue: None.

17.3 Paraffin Embedded Tissue Blocks/Slides

17.31 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from original surgery for NSCLC. **A corresponding H&E slide for each submitted block must be provided** to permit quality assessment of each tissue block.

17.32 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut 17 five micron sections (labeled 1-17) and mount on charged glass slides AND cut 5 ten micron sections (labeled 18-22) and mount on uncharged glass slides. **Label the slides with ACCRU patient ID number, accession number, order of sections (i.e., 1-22) and thickness of section (i.e., 5 or 10 micron).** H&E stain every 10th slide (i.e., slides labeled 1, 11). These H&E slides will be reviewed centrally under the research base's protocol for assessing tissue quality. The remaining unstained slides will be processed as described in 17.5. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**

17.33 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E slide (OR unstained slides with corresponding H&E(s) per table in Section 17.11 above).
- Research Tissue Submission Form
- Surgical Pathology Report
- Operative Report *(optional)*

Note: Please include the ACCRU patient ID number on all materials listed above.

17.34 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.

17.35 Tissue specimens must be shipped ≤30 days after registration.

17.36 Verify that the appropriate sections of the Research Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Research Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.37 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:

ACCRU Operations Office
[redacted]

17.38 If a corresponding H&E wasn't submitted with the block/slides, the ACCRU Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block and forwarded the cytotechnologist, Hilton 10, to be reviewed under the research base's protocol for assessing tissue quality for the proposed correlative studies, unless the tumor size is too small. If the tumor tissue is too small, assessment of tissue quality will occur at the time the translational studies are performed.

17.39a After the pathologist assesses the tissue quality, the block and appropriate paperwork will be returned to the ACCRU Operations Office.

17.39b When an appropriate request is submitted, the ACCRU Operations Office will forward the blocks/slides to the Dana Farber Cancer Institute Translational Research Laboratory [redacted] for processing as outlined in Section 17.5.

17.4 Frozen Tumor Tissue :None

17.5 Study Methodology and Storage Information

17.51 A secondary goal of this study is to determine whether the pre-existence of the EGFR T790M drug resistance mutation predicts for a worse clinical outcome with EGFR inhibitor therapy. EGFR T790M was first identified in 2004 as a co-mutation with L858R in a pretreatment lung cancer specimen, one of 111 EGFR-mutant tumors studied.[Kosaka *et al.*, 2004] In 2006, it was shown that with more sensitive testing methods (mutant-enriched PCR) T790M could be found in 4% of pretreatment EGFR-mutant lung cancers,[Inukai *et al.*, 2006] and these cases were found to not respond to TKI. More recently, both Maheswaran et al and Rosell et al found that, with multiple cycles of DNA amplification, highly sensitive assays could detect a T790M co-mutation in as many as 38% of baseline specimens,[Maheswaran *et al.*, 2008, Rosell *et al.*, 2011] making it a potential biomarker of poorer outcome on TKI. However, these studies were both performed with techniques that can be associated with false positive results thus obscuring the potential clinical relevance of this mutation if detected from a pre-treatment tumor specimen.

In the current study we will evaluate EGFR T790M from pre-treatment specimens using techniques that are optimized to prevent false positive amplifications of T790M. These include the use of a locked nucleic acid (LNA) to block amplification of wild-type DNA allows identification of T790M in as little as 0.1% of DNA (Arcila, CCR, 2011). A new T790M assay developed at DFCI and by Transgenomic Inc. and uses coamplification at a lower denaturation temperature (COLD)-PCR.[Li *et al.*, 2009] By further blocking amplification of wild-type DNA, this technique could prevent the appearance of false peaks and reduce the risk of false positive results.

We will evaluate the prevalence of EGFR T790M from pre-treatment tumor specimens. In addition, we will correlate the outcome of patients (as measured by progression free survival) with and without evidence of pre-treatment T790M in each arm of the study. The ability to perform these studies will be dependent on the pre-treatment prevalence of EGFR T790M in patients enrolling in this clinical trial.

Submitted tissue samples will be analyzed as follows:

17.52 FFPE tumor tissue blocks/slides will be collected in order to assess the prevalence of baseline EGFR T790M and to correlate the findings with progression free survival in each of the treatment arms. The H&E slides will be reviewed by a cytotechnologist to assess tumor content of the specimen. Appropriately identified tumor sections will then be used to isolate DNA. The analyses for EGFR T790M will be performed in Dr. Jänne's laboratory at the Dana Farber Cancer Institute. They will be performed in a blinded fashion without knowledge of patient outcome or treatment arm of the study.

17.53 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations Office (attn: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.16). Potential future research may include immunohistochemistry (IHC) analyses, DNA extraction, and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. For TMAs, the donor block remains intact except for 6 small (0.6mm) holes where the cores were taken. This process has minimal impact on the utility of the block for future clinical diagnostic needs. When a protocol is developed, it will be presented for IRB review and approval.

17.54 Banking of tumor tissue, according to the patient consent permission (see Section 6.5), is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for Mayo Clinic Cancer Center lung studies.)

17.55 The institutional pathologist will be notified by the ACCRU Operations Office (Pathology Coordinator) if the block may be depleted.

17.56 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.6 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sough regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s) -

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study Form	≤2 weeks after registration
Baseline Adverse Event Form	
Pretreatment RECIST Measurement Form	
Baseline Research Blood Submission Form (see Section 14.0)[2]	
Baseline Research Tissue Submission Form (see Section 17.0)	
OP and Path Reports (see Section 17.0)[1]	
CD Submission Form[3]	
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Submit copy to the ACCRU Ops Office, Attn. QAS for RC1126. This is in addition to the pathology material requirements for tissue submission (Section 17.0).
2. Submit ≤1 day after specimen collection.
3. Submit relevant radiographic images as a digital image (via CD) with a viewing tool free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s) of tumor response at baseline and tumor response and/or progression. Submit CD's labeled with study number (RC1126), ACCRU patient ID, patient initials, and visit date to the [redacted]

Test Schedule Material(s) -

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation (All Patients)
Evaluation/Treatment Form	X[3]	X	
Evaluation/Observation Form			X[2]
Adverse Event Form	X	X	X
RECIST Measurement Form	X[1,4]	X[1,4]	X[1,4]
Research Blood Submission Form	X (see Section 14.0)		
CD Submission Form[5]	At each occurrence[5]		
End of Active Treatment/Cancel Notification Form		X	
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)		
ADR/AER	At each occurrence (see Section 10.0)		

1. Submit copy of documentation of response or progression to the [redacted]
2. Complete at each evaluation during Observation (see Section 4.0).
3. Complete at each evaluation during Active Treatment (see Section 4.0).
4. Patients should undergo imaging for disease progression every 2 cycles for the initial 18 months, then after 18 months every 4 cycles until disease progression.
5. Submit relevant radiographic images as a digital image (via CD) with a viewing tool free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s) of tumor response at baseline and tumor response and/or progression. Submit CD's labeled with study number (RC1126), ACCRU patient ID, patient initials, and visit date to the [redacted]

Follow-up Material(s) -

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 6 mos.	Death	New Primary
Event Monitoring Form[3]	X[2]	X[2]	X	X	At each occurrence

1. If a patient is still alive 6 years after randomization, no further follow-up is required.
2. Submit copy of documentation of response or progression to the ACCRU Operations Office, Attention: [redacted]
3. If patient discontinues treatment due to PD, complete the Event Monitoring Form at the time of PD and then complete Observation (21-42 days after treatment discontinuation) phase and continue on the Event Monitoring Phase.

19.0 Budget

19.1 Costs charged to patient: Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: Research blood kits/collection and tissue collection.

19.3 Other budget concerns: Bevacizumab and erlotinib will be provided free of charge by Genentech.

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