SYNOPSIS OF CLINICAL STUDY REPORT

Name of Sponsor/Company: Genentech, Inc.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
Name of Finished Products: Bevacizumab and Erlotinib	**Volume:**	
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Title of Study:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE IIIb TRIAL COMPARING BEVACIZUMAB THERAPY WITH OR WITHOUT ERLOTINIB AFTER COMPLETION OF CHEMOTHERAPY WITH BEVACIZUMAB FOR THE FIRST-LINE TREATMENT OF LOCALLY ADVANCED, RECURRENT, OR METASTATIC NON–SMALL CELL LUNG CANCER**
Phase of Development:	IIIb
Investigators:	A list of investigators is provided in Appendix 16.1.4.
Study Centers:	There were a total of 187 study sites in the United States, Europe, and the rest of the world.
Publications:	No publications have resulted from this study.
Study Period:	10 January 2006 to 19 June 2009 (database cutoff)

Objectives

Primary:

- To compare progression-free survival (PFS) in patients with non–small cell lung cancer (NSCLC) randomized to bevacizumab + erlotinib versus bevacizumab + placebo following completion of four cycles of chemotherapy and bevacizumab without disease progression or significant toxicity.

Secondary:

- Among all enrolled patients, to evaluate the safety of bevacizumab during the chemotherapy phase by chemotherapy regimen and overall as measured by the incidence of selected Grade ≥ 3 adverse events
- Among patients who completed four cycles of chemotherapy and bevacizumab and underwent randomization, to evaluate the safety of bevacizumab + erlotinib versus bevacizumab + placebo during the post-chemotherapy phase, as measured by the incidence of all adverse events
- Among all enrolled patients, to evaluate the safety of bevacizumab for both phases of therapy by chemotherapy regimen and overall as measured by the incidence of selected Grade ≥ 3 adverse events
- Among all enrolled patients, to evaluate the incidence of treatment discontinuation for reasons other than disease progression during both phases of therapy
- Among patients who completed four cycles of chemotherapy and bevacizumab and underwent randomization, to compare the overall survival of the group receiving bevacizumab + erlotinib versus bevacizumab + placebo

  Overall survival was defined as the length of time from randomization to death.

The following secondary objective was included in the interest of interpreting results in the context of Study E4599, in which overall survival was established from the time of initiation of first-line therapy:

- Among all enrolled patients, to estimate overall survival in the two treatment arms: chemotherapy + bevacizumab followed by bevacizumab + erlotinib versus chemotherapy + bevacizumab followed by bevacizumab + placebo

  Overall survival was defined as the length of time from enrollment to death.

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Methodology

This was a Phase IIIb, multicenter, randomized, placebo-controlled trial to evaluate the safety and efficacy of chemotherapy + bevacizumab followed by bevacizumab + erlotinib versus bevacizumab + placebo in patients with locally advanced, recurrent, or metastatic NSCLC. The trial contained two treatment phases. The first phase (chemotherapy phase) was conducted in an open-label fashion; the second phase (post-chemotherapy phase) contained two treatment arms and was conducted in a randomized, double-blind, placebo-controlled fashion. At the end of the chemotherapy phase, patients who had not developed progressive disease continued on to the post-chemotherapy phase.

During the chemotherapy phase, investigators chose one of six chemotherapy regimens (see Section 9.4.1). Bevacizumab was administered immediately following chemotherapy on Day 1 of each cycle.

For the post-chemotherapy phase, only patients who completed four cycles of chemotherapy + bevacizumab without disease progression or significant toxicity were eligible for randomization, on the basis of stratification factors, to one of two treatment arms:

- Arm 1: bevacizumab (15 mg/kg on Day 1 of every 21-day cycle) plus placebo
- Arm 2: bevacizumab (15 mg/kg on Day 1 of every 21-day cycle) plus erlotinib (150 mg orally daily)

Prior to Amendment 4, patients who experienced disease progression during the chemotherapy or post-chemotherapy phases could receive optional post-progression therapy consisting of bevacizumab and/or erlotinib. Upon enactment of Amendment 4, patients who experienced disease progression during the chemotherapy or post-chemotherapy phases were discontinued from study treatment (i.e., they no longer had the option of entering the optional post-progression phase). Patients who had already begun optional post-progression therapy prior to Amendment 4 continued to have bevacizumab and/or erlotinib provided by the Sponsor until further disease progression.

Survival follow-up information was collected every 3 months prior to enactment of Amendment 4. After implementation of Amendment 4, survival was followed only for 30 days after treatment discontinuation.

Number of Patients (Planned and Analyzed):

Planned enrollment: 1150 patients

Actual enrollment: 1145 patients enrolled into the chemotherapy phase, with 743 randomized to one of two treatment arms in the post-chemotherapy phase

Diagnosis and Main Criteria for Inclusion:

Patients ≥ 18 years of age with advanced NSCLC without prior systemic treatment for locally advanced, recurrent, or metastatic disease were eligible for enrollment in this study. This included patients with Stage IIIB with malignant pleural effusion or Stage IV or recurrent disease. Patients with squamous cell carcinoma were eligible provided that their disease was extrathoracic or that their intrathoracic disease consisted of peripheral lesions only. Patients with a history of brain metastases were eligible as long as their brain metastases had been treated, and they did not have an ongoing requirement for treatment with dexamethasone at screening.

Test Product, Dose and Mode of Administration, Batch Number:

Patients randomized to Arm 1 received erlotinib placebo tablets in addition to bevacizumab. Patients randomized to Arm 2 received erlotinib 150 mg orally daily.

The dose of erlotinib may have been reduced as described in the protocol: the first reduction was to 100 mg/day, and the second reduction was to 50 mg/day.

Batch numbers are provided in Appendix 16.1.6.

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Duration of Treatment:

In the chemotherapy phase, patients received bevacizumab in combination with the investigator's choice of chemotherapy for a maximum of four 21-day cycles, or until disease progression or significant toxicity. Eligible patients then entered the post-chemotherapy phase, during which they received bevacizumab in combination with erlotinib or placebo until disease progression of significant toxicity.

Reference Therapy, Dose and Mode of Administration, Batch Number:

In the chemotherapy phase, all patients received an intravenous (IV) chemotherapy regimen selected by the investigator (see Section 9.4.1) plus bevacizumab 15 mg/kg by IV infusion on Day 1 of every 21-day cycle.

In the post-chemotherapy phase, all patients received bevacizumab 15 mg/kg by IV infusion on Day 1 of every 21-day cycle.

No reductions in the bevacizumab dose were allowed during the study. If an adverse event occurred that necessitated holding the bevacizumab dose, the dose remained unchanged once treatment resumed.

Chemotherapy dose modification for toxicity was to follow institutional standards. Investigators may have also referred to the respective approved labeling for recommendations from the manufacturer and local health authorities.

Bevacizumab batch numbers are provided in Appendix 16.1.6.

Criteria for Evaluation

Efficacy:

Efficacy analyses and analyses of study conduct, demographic/baseline characteristics, and tumor characteristics were based on randomized patients. Patients were analyzed as randomized with respect to the assignment of erlotinib or placebo.

Safety:

Safety analyses for the chemotherapy phase were based on safety-evaluable enrolled patients. Patients were analyzed as treated, with respect to the assignment of erlotinib or placebo.

Other safety populations included subsets of the patients treated with any study drug, the anticoagulated population, squamous population, and brain metastases population.

Statistical Methods

Primary Endpoint:

The primary efficacy analysis of bevacizumab + erlotinib (Arm 2) compared with bevacizumab + placebo (Arm 1) evaluated PFS in the post-chemotherapy phase.

PFS was defined as the length of time from randomization until documented disease progression or death from any cause, whichever occurred earlier. Disease progression was assessed by the investigator according to the Response Evaluation Criteria for Solid Tumors (RECIST). Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression were not considered to have disease progression (i.e., clinical progression was not considered as an event per RECIST). Tumor measurements from the pre-randomization assessment served as the baseline for determining progression.

PFS was tested using a two-sided stratified log-rank test with an overall $\alpha = 0.05$. The stratification factors consisted of sex, smoking history (never vs. prior/current), ECOG performance status from

pre-randomization assessment (0 vs. ≥ 1), and initial chemotherapy regimen (carboplatin + paclitaxel vs. carboplatin + gemcitabine vs. carboplatin + docetaxel vs. cisplatin + gemcitabine vs. other chemotherapy regimens). Results from an unstratified log-rank test are also presented. Kaplan–Meier methodology was used to estimate median PFS for each treatment arm. Kaplan–Meier curves were constructed to provide a visual description of the difference between the two treatment arms.

The hazard ratio for PFS was estimated using a stratified Cox regression model with the same stratification factors as used in the stratified log-rank test. The unstratified hazard ratio is also presented.

Several sensitivity analyses for PFS were performed.

Secondary Endpoints:

The secondary efficacy analysis compared overall survival in patients randomized to bevacizumab + erlotinib versus bevacizumab + placebo. Overall survival was defined as the time from randomization until death from any cause.

Overall survival was tested using a two-sided stratified log-rank test with an overall $\alpha = 0.05$. The stratification factors consisted of sex, smoking history (never vs. prior/current), ECOG performance status from pre-randomization assessments (0 vs. ≥ 1), and initial chemotherapy regimen (carboplatin + paclitaxel vs. carboplatin + gemcitabine vs. carboplatin + docetaxel vs. cisplatin + gemcitabine vs. other chemotherapy regimens). Results from an unstratified log-rank test were also presented. The hazard ratio for overall survival was estimated using a stratified Cox regression model with the same stratification factors used in the stratified log-rank test. The unstratified hazard ratio was also presented.

Kaplan–Meier methodology was used to estimate median overall survival for each treatment arm, and Kaplan–Meier curves were constructed to provide a visual description of the difference between the treatment arms.

Summary of Results and Conclusions

The following summary is based on the 18 July 2008 data cutoff, the definitive analysis for efficacy and safety. Updated safety and overall survival analyses were performed using a later cutoff, and the results were similar.

Efficacy and Pharmacokinetic/Pharmacodynamic Conclusions:

- The addition of erlotinib to bevacizumab, after four cycles of chemotherapy and bevacizumab, resulted in a statistically significant improvement in PFS for patients with locally advanced, recurrent, or metastatic NSCLC who had completed four cycles of chemotherapy and bevacizumab without disease progression or significant toxicity (stratified analysis: HR = 0.708; log-rank p = 0.0006).
- A PFS benefit from the addition of erlotinib to bevacizumab was consistently observed in pre-specified subgroups defined by stratification factors (sex, smoking history, ECOG performance status at randomization, and the initial chemotherapy regimens) and demographic and other baseline characteristics.

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- Biomarkers, including EGFR (IHC), *EGFR* (FISH), and *K-ras* mutation status, were not strongly predictive of outcome. However, benefit in terms of PFS was observed across most biomarker subgroups, and patients with EGFR-activating mutations in the Bev + Er arm showed considerable PFS improvement relative to those in the Bev + Pl arm (HR = 0.44; 95% CI: 0.22, 0.86). These results should be interpreted with caution given the small sample size and exploratory nature. Overall survival analyses were not able to identify a specific patient subgroup with overall survival benefit.
- The consistency of results of the sensitivity and subgroup analyses for the primary endpoint of PFS demonstrated the robustness of the treatment effect.
- A statistically significant difference in overall survival was not detected between treatment arms (stratified analysis: HR = 0.917; log-rank p = 0.5341).
- Overall survival from enrollment (median overall survival: 12.9 months in the Bev + Pl arm at the 18 July 2008 data cutoff) was comparable to results from Study E4599.
- Two exploratory analyses of overall survival were performed at the 28 January 2009 data cutoff (stratified analysis: HR = 0.904; log-rank p = 0.3534) and the 19 June 2009 data cutoff (stratified analysis: HR = 0.897; log-rank p = 0.2665). The numerical improvement in overall survival seen with longer follow-up was not statistically significant.

Safety Conclusions:

Chemotherapy Phase

- These data indicate an acceptable safety profile for bevacizumab when given in combination with a variety of chemotherapy regimens. The safety profile is similar to that reported in previous Phase III trials in non-squamous NSCLC.
- The incidence of serious adverse events was 35.8% in the Carbo + Doc group, 29.8% in the Carbo + Pac group, 31.3% in the Carbo + Gem group, and 26.0% in the Cis + Gem group. The majority of serious adverse events were Grade 3 or 4.
- A total of 161 patients (14.1%) discontinued bevacizumab because of an adverse event. A total of 108 patients (9.4%) discontinued chemotherapy because of an adverse event.
- Grade ≥ 3 adverse events of special interest evaluated for the chemotherapy phase were hemorrhage, GI perforation, hypertension, proteinuria, ATE events, CHF, and infection categories. The overall incidence of these events was low, independent of chemotherapy regimen. The most common events were infection (7.0%), hypertension (3.8%), and hemorrhage (3.2%).
- Sixteen patients (1.4%) experienced a Grade ≥ 2 pulmonary hemorrhage during the chemotherapy phase.
- A total of 50 patients (4.4%) died within 30 days following the last study treatment in the chemotherapy phase. Among these, 27 patients (2.4%) died as the result of a serious adverse events.

Post-Chemotherapy Phase

- The addition of erlotinib to bevacizumab was associated with an increase in the incidence of all adverse events (95.9% vs. 86.9%) and Grade 3 and 4 adverse events (46.2% vs. 33.2%). The incidence of serious adverse events was also higher in the Bev + Er arm than in the Bev + Pl arm (23.4% vs. 17.2%).

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- Adverse events of any grade occurring at a ≥5% higher incidence in the Bev + Er arm than in the Bev + Pl arm were rash, diarrhea, fatigue, nausea, anorexia, dermatitis acneiform, dry skin, weight decreased, depression, and mucosal inflammation.
- The incidence of adverse events of special interest was generally similar between the two treatment arms, with the exception that higher rates were observed in the Bev + Er arm for rash (62.8% vs. 22.3%), diarrhea (51.6% vs. 19.9%), and infection (30.4% vs. 25.3%). Adverse events of special interest were predominantly Grade 1 or 2.
- There were a total of 6 Grade 5 adverse events of special interest: 2 in the Bev + Pl arm (CHF and lobar pneumonia) and 4 in the Bev + Er arm (cardiac arrest [n = 2], cerebellar infarction, and deep vein thrombosis). One additional Grade 5 event (GI perforation) was reported in the Bev + Er arm after the 18 July 2008 data cutoff.
- The incidence of Grade 3 or 4 adverse event of special interest (other than rash and diarrhea) was similar in the two treatment arms: hypertension occurred at a similar incidence in the two treatment arms (6.0% in the Bev + Pl arm vs. 6.3% in the Bev + Er arm), as did infection (4.9% in the Bev + Pl arm vs. vs. 4.6% in the Bev + Er arm). There were no reported Grade 3 or 4 ILD-like events in the Bev + Pl arm, whereas 3 patients (0.8%) in the Bev + Er arm experienced a Grade 3 ILD-like event.
- The incidence of adverse events leading to erlotinib/placebo discontinuation was higher in the Bev + Er arm (17.1%) than in the Bev + Pl arm (12.3%).
- The incidence of adverse events leading to bevacizumab discontinuation during the post-chemotherapy phase was similar in the two treatment arms (13.9% in the Bev + Pl arm vs. 13.3% in the Bev + Er arm), and most adverse events leading to bevacizumab discontinuation occurred at a < 1% incidence, with the exception of deep vein thrombosis (1%).
- The incidence of adverse events of special interest leading to erlotinib/placebo discontinuation during the post-chemotherapy phase was increased in the Bev + Er arm mainly as the result of ATE events (0.3% vs. 1.1%), rash (1.4% vs. 2.2%), diarrhea (1.1% vs. 2.2%), and infection (0.8% vs. 1.4%).
- The incidence of adverse events of special interest leading to bevacizumab discontinuation in the post-chemotherapy phase was similar in the two treatment arms and was < 1%, with the exception of hemorrhage (1.9% vs. 1.6%), pulmonary hemorrhage (1.1% vs. 1.4%), ATE events (1.1% vs. 1.9%), and VTE events (1.4% vs. 0.8%) in the Bev + Pl arm versus Bev + Er arm, respectively.
- The number of treatment-related deaths was higher in the Bev + Er arm (1.1% in the Bev + Pl arm vs. 2.2% in the Bev + Er arm).

Overall Conclusions:

The results of this study support the following conclusions:

- The addition of erlotinib to bevacizumab after four cycles of bevacizumab and chemotherapy led to a statistically significantly improvement in PFS (HR = 0.708; p = 0.0006) for patients who had not progressed during chemotherapy. Median PFS was 3.7 months and 4.8 months for the Bev + Pl and Bev + Er arms, respectively.
- The PFS improvement was consistent across multiple subgroups, including those defined by sex, histology, age, and smoking status.

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- Biomarkers, including EGFR (IHC), *EGFR* (FISH), and *K-ras* mutation status, were not strongly predictive of outcome. However, benefit in terms of PFS was observed across most biomarker subgroups, and patients with EGFR-activating mutations in the Bev + Er arm showed considerable PFS improvement relative to those in the Bev + Pl arm (HR = 0.44; 95% CI: 0.22, 0.86).
- The addition of erlotinib to bevacizumab after four cycles of chemotherapy and bevacizumab did not result in a statistically significant improvement in overall survival for patients who had not progressed during chemotherapy.
- In the chemotherapy phase, the safety profile of bevacizumab was acceptable when given in combination with a variety of common chemotherapy regimens used for the first-line treatment of patients with locally advanced, recurrent, or metastatic NSCLC.
- The addition of erlotinib to bevacizumab in the post-chemotherapy phase was associated with an increased incidence of all adverse events, Grade 3 and 4 adverse events (especially rash and diarrhea), and serious adverse events.
- The incidence of adverse events leading to erlotinib discontinuation during the post-chemotherapy phase was increased in the Bev + Er arm, as the result of a higher incidence of discontinuations due to rash and diarrhea.
- The incidence of adverse events leading to bevacizumab discontinuation during the post-chemotherapy phase was comparable in the two treatment arms and consistent with the known profile of bevacizumab in NSCLC.

The addition of erlotinib to bevacizumab resulted in an improvement in PFS; however, because no improvement in overall survival was seen and the regimen was associated with increased toxicity, the benefit–risk profile of this combination needs to be carefully evaluated against other available treatments.

Date of the Report

24 November 2010