Official Title: A Phase III, Multicenter, Placebo-Controlled, Double-Blind, Randomized Clinical Trial to Evaluate the Efficacy of Bevacizumab in Combination With Tarceva® (Erlotinib) Compared With Tarceva Alone for Treatment of Advanced Non−Small Cell Lung Cancer (NSCLC) After Failure of Standard First-Line Chemotherapy

NCT Number: NCT00130728

Document Date: Protocol Version A6: 11-October-2012

TITLE:	**A PHASE III, MULTICENTER, PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY OF BEVACIZUMAB IN COMBINATION WITH TARCEVA® (ERLOTINIB) COMPARED WITH TARCEVA ALONE FOR TREATMENT OF ADVANCED NON–SMALL CELL LUNG CANCER (NSCLC) AFTER FAILURE OF STANDARD FIRST-LINE CHEMOTHERAPY**
PROTOCOL NUMBER:	OSI3364g
VERSION NUMBER:	A6
IND NUMBER:	7023
TEST PRODUCT:	Bevacizumab (RO4876646) and Erlotinib (RO508231)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 2 February 2005
DATES AMENDED:	Version A1: 26 April 2005 Version A2: 31 October 2005 Version A3: 3 March 2006 Version A4: 30 November 2006 Version A5: 12 March 2009 Version A6: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	11-Oct-2012 05:38:38

PROTOCOL AMENDMENT, VERSION A6:
RATIONALE

The results of the final analysis of the BETA Lung trial (OSI3364g), an international, randomized, placebo-controlled, Phase III trial, were presented at the 2008 Chicago Lung meeting by Dr. John Hainsworth on behalf of the BETA investigators. The addition of bevacizumab to erlotinib in the BETA lung study provided evidence of clinical activity by doubling progression free survival and the overall response rate. However, this clinical benefit was not associated with an improvement in survival.

At the time of this amendment, there are 4 patients receiving single-agent erlotinib in this study. All of the patients remaining in the study are located in the United States.

Protocol Study OSI3364g has been amended because the study has been completed and no further patient data will be collected, except for serious adverse event reporting via MedWatch Food and Drug Administration 3500 Forms, no longer with the CRFs, and will be handled according to instructions in Section 5.4 .

Additional changes to the protocol are as follows:

- Despite being unblinded in 2008, some patients are still receiving study drugs from treatment bottles assigned via the interactive voice response system labeled as “OSI-774 25mg, 100mg or 150mg” as per study protocol. Upon enactment of this amendment, patients will be receiving study drugs directly from Astellas Pharma US, Inc. labeled as “erlotinib” at their current dosage.
- Upon enactment of Amendment 6, no dose adjustments will be permitted. Any patient requiring a dose modification because of an adverse event or disease progression should be terminated from the study and treated following the physican’s usual standard of care.

The sample Informed Consent Form has also been revised to reflect the changes to the study protocol.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION A6:

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 2.2: SECONDARY OBJECTIVES

The secondary objectives of this Phase III study were as follows:

- To evaluate the safety of combining bevacizumab with Tarceva in patients with previously treated advanced NSCLC, including patients with squamous cell carcinoma, patients with treated brain metastases, and patients receiving full-dose anticoagulation with low-molecular-weight heparin or fondaparinux.

  Note: See Section 4.1.2 for the eligibility criteria regarding squamous cell carcinoma patients.

  ~~*Note: The safety profile of patients who remain on protocol treatment at the enactment of amendment 5 will be evaluated to better characterize the long term safety of the bevacizumab and erlotinib combination.*~~

  Note: Upon enactment of Amendment 6, safety data collection will be restricted to the reporting of serious adverse events via MedWatch FDA 3500 forms (Appendi x D) and will not be captured in the CRF.

SECTION 3.3.4: Safety Outcome Measures

The safety outcome measures for this study were the following:

- Incidence and severity of adverse events and serious adverse events
- Changes in laboratory values

~~*Patient safety after Amendment 5 will be assessed through summaries of serious adverse events.*~~

Patient safety after Amendment 6 will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

SECTION 3.4: SAFETY PLAN

Upon enactment of Amendment 6, data collection will be restricted to reporting of serious adverse events via MedWatch FDA 3500 forms (not in the CRF), and handled according to instructions in Section 5.4. SAE data will be collected via the safety database only. Prior to Amendment 6, the safety plan was as below.

See Section 4.3.4and Section 5 for complete details of the safety evaluation for this study.

A number of measures have been taken to ensure the safety of patients participating in this study. These measures were addressed through the exclusion criteria (see Section 4.1.3) and routine monitoring as follows.

Patients enrolled in this study were evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations consisting of medical interviews, recording of concomitant medications and adverse events, physical examinations, blood pressure, and laboratory measurements (performed by local laboratories, see Section 4.5 and Appendix A) have been conducted. Patients have been evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit while on study drug. Patients discontinued from the treatment phase of the study for any reason were evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 4.5.3). Patients with an ongoing Grade 4 or serious adverse event at the time of discontinuation from study treatment were *and* ~~will continue to be~~ followed until the event is resolved or determined to be irreversible by the investigator (see Section 4.5.3).

Specific monitoring procedures were as follows:

- Hypertension was monitored through routine evaluation of blood pressure.
- In patients with bleeding, a hemostasis evaluation was performed as clinically indicated. In patients with hemoptysis, bevacizumab should be permanently discontinued and protocol guidelines followed (see Section 4.3.4 and Table 2). Early use of bronchoscopy to identify the site of bleeding should also be considered.
- Patients with a history of brain metastases were monitored for the development of symptomatic Grade $\geq$ 2 CNS hemorrhage (NCI CTCAE, Version 3.0). Symptomatic is defined as clinical symptoms that are determined by the investigator to be directly referable to a CNS hemorrhage. Bevacizumab should be discontinued and protocol guidelines followed in patients who develop symptomatic Grade $\geq$ 2 CNS hemorrhage (see Section 4.3.4 and Table 2).
- Patients requiring full-dose anticoagulation could be treated with low-molecular-weight heparin or fondaparinux; these patients were and have been monitored for Grade $\geq$ 3 hemorrhage events. Full-dose anticoagulation with warfarin is prohibited; however, prophylactic doses were allowable.
- Bevacizumab should be discontinued and protocol guidelines followed in patients who develop symptomatic Grade $\geq$ 2 CNS hemorrhage or Grade $\geq$ 3 hemorrhage (see Section 4.3.4 and Table 2).
- Because of the potential for drug–drug interaction between Tarceva and warfarin, patients who received concomitant prophylactic/low-dose warfarin therapy were to be monitored closely for INR changes or bleeding.
- Chronic use of full-dose nonsteroidal anti-inflammatory drugs (NSAIDs) was not allowed while on study treatment. If required, the patient must be discontinued from bevacizumab/placebo.

- Aspirin up to, but not exceeding, 325 mg per day could be given to patients at high risk for arterial thromboembolic disease. Patients developing signs or symptoms of arterial thromboembolic events (see Table 2) while on study treatment were asked to discontinue bevacizumab/placebo.
- Proteinuria was monitored through regular urinalysis and urinary protein to creatinine ratio. Screening for proteinuria at ex-U.S. sites was performed with a urine dipstick (patients found to have ≥ 3+ proteinuria by dipstick had to undergo a 24-hour urine collection)
- Symptoms consistent with ILD, such as new onset dyspnea, cough, or fever without an obvious cause were to be evaluated. In the event that ILD was suspected, study treatment was to be discontinued and the patient given appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often provided. Tarceva should not be restarted in patients suspected of having drug-related ILD.
- NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving Tarceva therapy. Patients were asked to seek medical advice promptly if they experienced eye irritation during Tarceva therapy.

See Section 4.3.4 for detailed instructions about the management of study drug-related toxicities. The DMC monitored the safety of this study by reviewing serious adverse events every month and during the two interim analyses. Members of the DMC were external to Genentech and followed a charter that outlines the Committee's composition and the members' roles and responsibilities.

~~*Safety monitoring for patients who remain on study treatment after the final analysis will be conducted by Genentech or Genentech's agent.*~~

SECTION 3.7: ETHICAL CONSIDERATIONS

Genentech *performed* ~~*will perform*~~ safety reviews after the final analysis.

The final analysis of OSI3364g showed that the addition of bevacizumab to erlotinib improved PFS and ORR. However, this clinical benefit was not associated with an improvement in survival.

Amendment 5 *allowed* ~~*was designed to give*~~ investigators and patients who *had* ~~*have*~~ not progressed the option to continue active study treatment until disease progression, while continuing to provide long-term data on the safety of the bevacizumab and erlotinib combination.

Forty-eight patients remained on study treatment at the time of the final BETA analysis. Some had been on study for more than 1 year. The continued collection of safety information on these long-term non-progressing patients *allowed* ~~*will allow*~~ for a better description of the long-term safety profile of the bevacizumab and erlotinib combination.

All placebo treatment in the BETA trial will be discontinued to remove the risks and discomforts associated with infusion therapy.

Investigators and patients are not obligated to remain on study treatment. They may choose to discontinue trial participation given the failure of the study to meet its primary endpoint of improved overall survival.

Upon enactment of Amendment 6, data collection will be restricted to spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms (not in the case report form [CRF]), and handled according to instructions in Section 5.4. SAE data will be collected via the safety database only.

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Note: This study has been fully recruited and all subjects were unblinded to study drug following the final analysis. Upon enactment of Amendment 6, the interactive voice response system (IVRS) will be cancelled. Prior to enactment of Amendment 6, treatment assignment and unblinding were managed as below.

After written informed consent was obtained and eligibility established (with archival tissue identified and available for research testing), the study site obtained the patient's identification number and treatment assignment from the IVRS. Patients could be randomized up to 5 days prior to receiving their first dose of study treatment. A hierarchical dynamic randomization scheme was used to ensure an approximately equal sample size for the two treatment arms overall, within each of the four categories defined by baseline ECOG performance status (0/1 vs. 2) and smoking history (never vs. current/previous), within each sex, and within each study site.

Genentech, the investigator, and the patient were blinded to treatment assignment. Unblinding of treatment assignment prior to final study analysis was permitted only for a serious study drug–related toxicity. All cases of safety unblinding required the approval of the Medical Monitor. After the final analysis, unblinding information was provided to all sites with patients receiving study treatment. Unblinding information for patients who had completed study treatment prior to the final analysis was provided upon request.

If a patient discontinued Tarceva therapy because of unmanageable toxicity, an unblinding request could be made to determine the treatment assignment. Study bevacizumab/placebo was discontinued and subsequent therapy provided at the discretion of the treating clinician.

~~Requests for unblinding may be made by calling the Medical Monitor directly during business hours (PST) at the following telephone number:~~

~~Medical Monitor: [redacted], M.D.~~
~~Telephone No.: [redacted]~~

~~Alternate Contact: [redacted], *Pharm.D.*~~
~~Telephone No.: [redacted]~~

~~Approval of the request and unblinding of study drug assignment will occur only during business hours.~~

Any toxicities associated or possibly associated with bevacizumab treatment were and should be managed according to standard medical practice. Discontinuation of bevacizumab has no immediate therapeutic effect. Bevacizumab has a terminal half-life of 2–3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab. ~~The i~~*I*nvestigator*s* were allowed to hold administration of study drug while waiting for a decision on unblinding to be made.

SECTION 4.3.1: Formulation

b. Tarceva

Tarceva *will* ~~*continues to*~~ be supplied by *Astellas* ~~OSI~~ Pharmaceuticals *US on behalf of OSI Pharmaceuticals LLC*, Inc. and F. Hoffman*n*-La Roche, Ltd. The oral tablets are conventional, immediate-release tablets containing erlotinib as hydrochloride salt. In addition to the active ingredient (erlotinib), tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, magnesium stearate, and the film coating Opadry® White, which is composed of hypromellose, hydroxypropyl cellulose, and titanium dioxide. Tablets containing 25 mg, 100 mg, and 150 mg of Tarceva are available. *Erlotinib will be provided in a bottle.* Each bottle *will contain* ~~or blister pack *contains*~~ 30 tablets, a quantity sufficient for 4 consecutive weeks of dosing, with overage. For further details, see the Tarceva® Investigator Brochure or Package Insert (see Appendix B).

SECTION 4.3.3: Dosage Modification

Upon enactment of Amendment 6, no dose adjustments will be permitted. Any patient requiring a dose modification due to an AE or PD should be terminated from the study and treated following the physician's usual standard of care. Prior to Amendment 6, dose modifications were handled as below.

SECTION 4.3.4: Management of Toxicities Related to Study Treatment

Upon enactment of Amendment 6, no dose adjustments will be permitted. Any patient requiring a dose modification due to an AE or PD should be terminated from the study and treated following the physician's usual standard of care. Prior to Amendment 6, toxicities related to study treatment were managed were handled as below.

SECTION 4.4: CONCOMITANT AND EXCLUDED THERAPIES

Upon enactment of Amendment 6, no information on concomitant therapies will be collected. Prior to Amendment 6, information on concomitant therapies were collected as below.

SECTION 4.5: STUDY ASSESSMENTS

~~The conduct below was required during the BETA trial. This should be continued for all patients who remain on study treatment after the final analysis until Amendment 5 is approved. After the approval of Amendment 5, treatment assessments should be based on the investigator's clinical judgment or conducted in accordance with institutional guidelines.~~

Upon enactment of Amendment 6, data collection will be restricted to spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms, not in the CRF, and handled according to instructions in Section 5.4. Prior to Amendment 6, assessments were conducted as below.

SECTION 4.5.3: Study Treatment Discontinuation Visit

Following termination of the study no further information will be collected upon enactment of Amendment 6. Patients will be followed according to the physician's usual standard of care. Prior to Amendment 6, the study termination visit and follow-up assessments were conducted as below.

SECTION 4.8: STATISTICAL METHODS

The statistical methods noted below were utilized during the interim and final analyses for OSI3364g when appropriate. ~~*The safety of patients who remain on study after the final analysis will be monitored by Genentech or a company representative. See Section 4.8.8. Reporting of safety data after the final analysis is described in Section 5.5.*~~ *Upon enactment of Amendment 6, no further analysis will be done. Data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.*

SECTION 4.8.5: Safety Analyses

Upon enactment of Amendment 6, data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms (not in the CRF), and handled according to instructions in Section 5.4. Prior to Amendment 5 safety assessments were conducted as below.

Safety was assessed through summaries of adverse events and laboratory test results. Patients who receive any amount of study treatment will be included in the safety assessment. Safety results were summarized by the treatment patients actually received for all patients, for patients with squamous cell carcinoma, for patients with brain metastases treated prior to enrollment, and for patients receiving full-dose anticoagulation with low-molecular-weight heparin or fondaparinux.

Safety data collected after the final analysis ~~*will be*~~*was* reviewed and summarized for inclusion in the Investigator's Brochure by Genentech or Genentech's agent.

a. Adverse Events

As clinical data and AEs will no longer be collected in the clinical database, no AEs will be recorded on the CRF.

SECTION 4.8.8: Interim Analyses

~~*Genentech and or a company representative will monitor the safety of patients who remain on study after the final analysis. The focus will be on serious adverse events.*~~

Upon enactment of Amendment 6, data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

SECTION 5: ASSESSMENT OF SAFETY

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF. The plan below was utilized prior to the final analysis of OSI3364g.

~~***The plan below was utilized prior to the final analysis of OSI3364g. The assessment plan should be continued for all patients who remain on study treatment after the final analysis, unless stated otherwise.***~~

~~*Adverse event collection subsequent to the activation of Amendment 5 will be limited to the collection of serious adverse events (SAEs). The period of collection will end 30 days after study treatment discontinuation. This will focus the safety evaluation of the bevacizumab and Tarceva combination during this period on events of greatest clinical significance.*~~

SECTION 5.1.2: Serious Adverse Events

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

SECTION 5.2: METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF. The plan below was utilized prior to the final analysis of OSI3364g.

SECTION 5.3.2: Specific Instructions for Recording Adverse Events on the Case Report Form

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

SECTION 5.4: EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

For U.S. sites, any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an *MedWatch FDA 3500 form* ~~SAE CRF page~~ within ~~48~~ *24* hours as described below.

Medical Monitor: [redacted], M.D.
Telephone No.:
Alternative Telephone No.: (888) 835-2555

Investigators will submit written reports of all SAEs, regardless of attribution, to Genentech within ~~48~~ *24* hours of learning of the events. For initial SAE reports, investigators should record all case details that can be gathered within ~~48~~ *24* hours on a *MedWatch 3500 form* ~~SAE CRF page~~. The completed *MedWatch 3500 form* ~~SAE CRF page~~ and SAE Fax Cover Sheet should be faxed immediately upon completion to Genentech's Drug Safety Department at:

(650) 225-4682
or
(650) 225-5288

Relevant follow-up information should be submitted to Genentech's Drug Safety as soon as it becomes available and/or upon request.

~~For ex U.S. sites, serious adverse events and pregnancies occurring during this study, or which come to the attention of the investigator during the protocol-defined follow up period, should be reported immediately to the Sponsor or its designee. Contact details will be provided to the investigator prior to study start. The investigator will complete and submit one SAE CRF page for each SAE experienced by a patient.~~

Note: All non-U.S. sites were closed prior to the enactment of Amendment 6.

SECTION 5.5: TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

All ~~AEs and~~ SAEs that are encountered during the protocol-specified AE reporting period should be followed to their resolutions, or until the investigator assesses them as stable, or the patient is lost to follow-up. Resolution of ~~AEs and~~ SAEs (with dates) should be documented *via a MedWatch FDA 3500 form.* ~~on the appropriate AE or SAE CRF page and in the patient's medical record to facilitate source data verification. *After the activation of Protocol Amendment 5, this documentation should be according to institutional practice or investigator judgment in the case of adverse events. SAEs should continue to be documented as described in this protocol section.*~~

SECTION 6.2: STUDY COMPLETION

Study OSI3364g is considered complete and no further patient data will be collected, except for serious adverse event reporting via MedWatch FDA 3500 Forms, (not in the CRF), and will be handled according to instructions in Section 5.4

SECTION 6.3: INFORMED CONSENT

The Informed Consent Form has been revised to reflect the changes made to the protocol under Amendment 6. Following submission and IRB approval of Amendment 6, only those patients who are currently receiving study treatment will be required to be reconsented with the amended Informed Consent Form.

SECTION 6.5: STUDY MONITORING REQUIREMENTS

Upon enactment of Amendment 6, all necessary study monitoring and site management will be performed remotely.

SECTION 6.9: STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech *and Astellas Pharmaceuticals*. The recipient will acknowledge receipt of the drug by returning the ~~INDRR 1 form indicating shipment content and condition~~*enclosed paperwork that is received with study medication shipments*. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the Drug Inventory Log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure only after study drug reconciliation has been performed and disposal has been authorized by a Genentech representative. ~~Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.~~

PROTOCOL AMENDMENT ACCEPTANCE FORM

The Protocol Amendment Acceptance Form has been updated to include the current administrative contacts.

U.S. Sites:
[redacted]
PPD LLC
3151 South 17th Street
Wilmington, NC 28412
Telephone: [redacted]

~~Non U.S. Sites:~~
~~Covance~~
~~Attn:~~ [redacted]
~~6 Roxborough Way~~
~~Maidenhead, Berkshire~~
~~SL6 3UD United Kingdom~~

APPENDIX D: MedWatch Form FDA 3500

Appendix D has been appended to the protocol.

SAMPLE INFORMED CONSENT FORM ADDENDUM

The sample Informed Consent Form has been created to inform of the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY OF BEVACIZUMAB IN COMBINATION WITH TARCEVA® (ERLOTINIB) COMPARED WITH TARCEVA ALONE FOR TREATMENT OF ADVANCED NON–SMALL CELL LUNG CANCER (NSCLC) AFTER FAILURE OF STANDARD FIRST-LINE CHEMOTHERAPY**
PROTOCOL NUMBER:	OSI3364g
VERSION NUMBER:	A6
IND NUMBER:	7023
TEST PRODUCT:	Bevacizumab (RO4876646) and Erlotinib (RO508231)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the original form to the appropriate address provided below. Please retain a copy for your study files.

U.S. Sites:

[redacted]
PPD LLC
3151 South 17th Street
Wilmington, NC 28412
Telephone: [redacted]

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY OF BEVACIZUMAB IN COMBINATION WITH TARCEVA® (ERLOTINIB) COMPARED WITH TARCEVA ALONE FOR TREATMENT OF ADVANCED NON–SMALL CELL LUNG CANCER (NSCLC) AFTER FAILURE OF STANDARD FIRST-LINE CHEMOTHERAPY**
PROTOCOL NUMBER:	OSI3364g
STUDY DRUGS:	Bevacizumab Tarceva® (Erlotinib)
PHASE:	III
INDICATION:	Advanced NSCLC after failure of standard first-line chemotherapy
IND:	7023
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.

objectives

Primary Objective

The primary objective of this Phase III study was to evaluate the efficacy of combining bevacizumab with Tarceva (erlotinib) relative to Tarceva monotherapy in patients receiving second-line therapy for advanced NSCLC. Efficacy will be assessed by measuring overall survival.

The addition of bevacizumab to erlotinib in the BETA lung study was not associated with an improvement in overall survival. However, bevacizumab when combined with erlotinib improved progression-free survival (PFS) and overall response rate (ORR), demonstrating evidence of clinical activity.

Secondary Objectives

The secondary objectives of this Phase III study were as follows:

- To evaluate the safety of combining bevacizumab with Tarceva in patients with previously treated advanced NSCLC, including patients with squamous cell carcinoma, patients with treated brain metastases, and patients receiving full-dose anticoagulation with low-molecular-weight heparin or fondaparinux.

  Note: See Section 4.1.2 for the eligibility criteria regarding squamous cell carcinoma patients.

Upon enactment of Amendment 6, patients still benefiting from their treatment will continue to receive it until disease progression, but no CRF data will be collected anymore. Serious Adverse Events will be collected spontaneously via MedWatch FDA 3500 forms (Appendix D) and will no longer be captured in the CRF.

- To evaluate the efficacy of combining bevacizumab with Tarceva relative to Tarceva monotherapy in patients with previously treated advanced NSCLC, as measured by PFS, ORR, and duration of response
- To evaluate the pharmacokinetic behavior of Tarceva and the combination of bevacizumab with Tarceva in a subset of patients with previously treated advanced NSCLC
- To evaluate the association of survival, PFS, and treatment effect with markers of epidermal growth factor receptor (EGFR) expression, as measured by immunohistochemistry (IHC), EGFR gene copy number measured by fluorescence in situ hybridization (FISH), and other molecular markers of EGFR pathway activity in archival tissue samples

study Design

This is a Phase III, multicenter, placebo-controlled, double-blind, randomized study. Six hundred thirty-six patients were randomized in a 1:1 ratio to one of two treatment arms:

- Arm 1: Tarceva + placebo
- Arm 2: Tarceva + bevacizumab

Outcome MeasureS

Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study was overall survival, defined as the period from the date of randomization until the date of patient death from any cause.

The addition of bevacizumab to erlotinib in the BETA lung study was not associated with an improvement in overall survival. However, bevacizumab when combined with erlotinib improved PFS and ORR, demonstrating evidence of clinical activity. See Appendix C.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures were as follows:

- PFS, defined as the time from randomization to documented disease progression, as determined by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST), or death on study treatment, whichever occurs first
- Objective response, as determined by the investigator using RECIST
- Duration of objective response, defined as the period from the date of initial partial or complete response (as determined by the investigator using RECIST) until the date of disease progression or death from any cause on study treatment
- Evaluation of the relationship between molecular exploratory markers and efficacy outcomes

Pharmacokinetic Outcome Measures

The pharmacokinetic outcome measures for erlotinib and its metabolite (OSI-420) were as follows:

- Maximum concentration at steady state ($C_{max,ss}$)
- Time of the maximum concentration at steady state ($T_{max,ss}$)
- Minimum concentration at steady state ($C_{min,ss}$)
- Apparent clearance at steady state
- Area under the erlotinib time–concentration curve (AUC_{0-tau})

The pharmacokinetic outcome measures for bevacizumab were as follows:

- Maximum concentration (C_{max})
- Minimum concentration (C_{min})

Safety Outcome Measures

The safety outcome measures for this study were the following:

- Incidence and severity of adverse events and serious adverse events
- Changes in laboratory values

Upon enactment of Amendment 6, data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will no longer be captured in the CRF.

Safety Plan

Upon enactment of Amendment 6, data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will no longer be captured in the CRF. Prior to Amendment 6, the safety plan was as below.

Patients enrolled in this study were evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations consisting of medical interviews, recording of concomitant medications and adverse events, physical examinations, blood pressure, and laboratory measurements (performed by local laboratories, see Section 4.5 and Appendix A) have been conducted. Patients have been evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit while on study drug. Patients discontinued from the treatment phase of the study for any reason were evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 4.5.3). Patients with an ongoing Grade 4 or serious adverse event at the time of discontinuation from study treatment were followed until the event is resolved or determined to be irreversible by the investigator (see Section 4.5.3).

Study Treatment

The dose of bevacizumab in this study continues to be 15 mg/kg administered by IV infusion on the first day of each 3-week cycle (± 4 days; the interval between infusions must not be < 17 days). The bevacizumab dose should be based on the patient's weight at screening (within 7 days prior to randomization) and should remain the same throughout the study (± 5% dosing variation). If bevacizumab/placebo administration fell outside of the 4-day visit window, for reasons other than toxicity management, the site had to obtain a protocol waiver prior to the infusion. The patient's schedule was then adjusted so that the subsequent bevacizumab/placebo infusion was given 3 weeks after the re-scheduled infusion.

Protocol waivers are no longer required for changes in treatment. Changes in the treatment dose or schedule may be made based upon the investigator's judgment and the institutional guidelines of the site. Placebo dosing will be discontinued for all patients on the Tarceva and placebo arm of the trial without evidence of progression as of the enactment of BETA lung trial Amendment 5.

The initial bevacizumab/placebo dose was delivered over 90 (± 10) minutes as a continuous IV infusion on Day 0. If a patient experienced an infusion-associated adverse event, he or she could be pre-medicated for the next study drug infusion; however, the infusion time could not be decreased for the subsequent infusion. If the first infusion was tolerated without infusion-associated adverse events, the second infusion could be delivered over 60 minutes (± 10 minutes). If a patient experienced infusion-associated adverse events with the 60-minute infusion, all subsequent doses were to be given over 90 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions could be delivered over 30 ± 10 minutes. If a patient experienced infusion-associated adverse events with the 30-minute infusion, all subsequent doses were to be given over 60 minutes. If the patient continued to experience infusion-associated adverse events with the 90-minute infusion, the patient's symptoms were managed per institutional standard of care.

Upon enactment of Amendment 6, no dose adjustments will be permitted. If a patient needs a reduced dose, she/he will be withdrawn from the study and will be treated following the physician's usual standard of care

Concomitant Therapy AND CLINICAL PRACTICE

All concomitant medications administered within 14 days preceding the initial study treatment administration on this study through the 30-day Post–Study Treatment Discontinuation Visit were recorded. The reason(s) for treatment, dosage, and dates of treatment should have been reported to the investigator and recorded as instructed on the study-specific Case Report Forms (CRFs).

Patients using oral contraceptives, hormone replacement therapy, or other maintenance therapy were asked to continue their use. Patients received full supportive care, including hematopoietic growth factors, transfusions of blood and blood products, antibiotics, anti-emetics, etc., when appropriate. Use of anti-tumor therapies was permitted after study treatment discontinuation.

Patients who experience infusion-associated temperature elevations to $\geq$ 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, including $\leq$ 48 hours of treatment with corticosteroids.

It is recommended that patients with indwelling venous catheters receive prophylaxis against catheter thrombosis in accordance with the local standard of care. Full-dose anticoagulation using low-molecular-weight heparin or fondaparinux is permitted, starting either prior to study enrollment or during study participation. Because of a potential drug–drug interaction between Tarceva and warfarin, it is preferable that patients receive low-dose warfarin for this purpose. Patients receiving prophylactic or low-dose warfarin or its equivalent require close INR monitoring.

Because of the bleeding risk associated with bevacizumab, chronic use of aspirin at a dose of $>$ 325 mg/day and full-dose NSAIDs are to be avoided.

Prolonged use of systemic corticosteroids for the treatment of skin toxicities is discouraged. Patients who are taking corticosteroids for reasons other than skin toxicity at study entry may continue their use.

Statistical Methods

Primary Efficacy Analysis

Analyses of overall survival and PFS included all patients who were randomized. For objective response and clinical benefit, only patients with measurable disease at baseline were included in the analysis. For duration of response, only responders were included in the analysis. All analyses were based on the treatment arm to which patients were randomized.

The primary efficacy endpoint was overall survival, defined as the period from the date of randomization (as entered in the IVRS) until the date of patient death from any cause. All deaths were included, regardless of whether they occur during treatment or following treatment discontinuation. For patients who have not died, survival data were censored at the date of last contact.

The two-sided log-rank test, stratified by the randomization stratification factors, was used to perform hypothesis testing for assessing the primary study objective. The randomization stratification factors were ECOG performance status (0/1 vs. 2), smoking history (never vs. current/previous), sex (male vs. female), and study site; however, because of the large number of study sites in this trial, study sites will not be included in any efficacy analyses adjusted for randomization stratification factors. Levels of the stratification factors reported on the CRF were used in the analysis. A sensitivity analysis stratified using levels reported on the IVRS was performed. Both analyses were based on the treatment arm to which the patients have been randomized.

An interim efficacy analysis was conducted when approximately 67% of the required deaths (280 deaths) occurred. Overall survival was tested at the significance level determined using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary so that the overall type I error rate will be maintained at the 0.05 level. The DMC recommended that the study continue as planned. The final efficacy analysis was conducted when 418 deaths occurred.

The unstratified log-rank test was performed as a sensitivity analysis. The Kaplan-Meier methods were used to estimate median overall survival for each treatment arm. Cox

proportional hazard models, using two models (with and without stratification by the randomization stratification factors), were employed to estimate the hazard ratio (i.e., the magnitude of treatment effect and 95% CI).

Upon enactments of Amendment 6, all the remaining patients in the study receive single agent open-label erlotinib. No further analysis will be done.

Safety Analyses

Safety was assessed through summaries of adverse events and laboratory test results. Patients who receive any amount of study treatment will be included in the safety assessment. Safety results were summarized by the treatment patients actually received for all patients, for patients with squamous cell carcinoma, for patients with brain metastases treated prior to enrollment, and for patients receiving full-dose anticoagulation with low-molecular-weight heparin or fondaparinux.

Safety data collected after the final analysis will be reviewed and summarized for inclusion in the Investigator's Brochure by Genentech or Genentech's agent.

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

Missing Data

For overall survival, patients who were lost to follow-up were analyzed as censored observations on the date of last contact.

Details of the analyses of missing data were provided in the Statistical Analysis Plan.

Determination of Sample Size

This *was* a Phase III study to evaluate the efficacy and safety of bevacizumab in combination with Tarceva relative to Tarceva alone in advanced NSCLC. A 33% improvement in survival *was* considered a clinically significant outcome. To calculate the number of deaths required in this study, the following assumptions were made:

- Two-sided log-rank test
- 83% power at the 5% significance level
- Hazard ratio of bevacizumab + Tarceva versus control (Tarceva alone) of 0.75 corresponding to a 33% improvement in median overall survival from 8 to 10.67 months
- Median overall survival for the control arm is hypothesized based on data from Study BR.21, taking into account the difference in patient population.
- An interim efficacy analysis will be performed when 67% of the required deaths have occurred. The significance level will be determined using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary.
- Five percent of patients will withdraw consent for survival follow-up or will be lost to follow-up.

With these assumptions, 417 deaths were required for the final analysis.

Interim Analyses

The eligible patient population was expanded to include selected patients with squamous cell carcinoma, patients with brain metastases treated prior to enrollment, and patients receiving full-dose anticoagulation with low-molecular-weight heparin or fondaparinux. A DMC monitored the safety of these and all other patients on this trial. The DMC reviewed safety summaries prepared by an external statistical data coordinating center, including monthly serious adverse event reports and thorough interim safety reports. Members of the DMC were external to Genentech and followed a charter that outlined their role and responsibilities. Study personnel remain blinded to study results until the formal unblinding took place in October 2008.

All patients were monitored clinically at 3-week intervals and radiographically at 6-week intervals through Week 24, at which point scans were followed at 12-week intervals. Patients

with a history of brain metastases also under went head CT scans or MRI scans every 6 weeks after Day 0 (beginning at Week 6) through Week 24 and then every 12 weeks thereafter. Summaries of collected serious adverse events were reviewed by the DMC monthly for all patients, for patients with squamous cell carcinoma, and for patients with brain metastases treated prior to enrollment.

All NCI CTCAE Grade $\geq$ 3 hemoptysis and symptomatic Grade $\geq$ 2 CNS hemorrhage events were to be reported as serious adverse events. Grade $\geq$ 3 hemoptysis events were closely monitored for patients with squamous cell carcinoma; enrollment for this subpopulation was to be discontinued if the incidence was unacceptable (for the stopping guidance, see the DMC charter). Symptomatic Grade $\geq$ 2 CNS hemorrhage events was closely monitored for patients with brain metastases treated prior to enrollment; accrual for this subpopulation was to be stopped if the incidence was unacceptable (for the stopping guidance, see the DMC charter). Symptomatic Grade $\geq$ 3 hemorrhage events was closely monitored for patients fully anticoagulated with low-molecular-weight heparin or fondaparinux; accrual for this subpopulation was to be stopped if the incidence of such events was unacceptable.

Two interim analyses were conducted. The first interim analysis was conducted after 123 patients had been enrolled and followed for at least 2 months. Only safety data were assessed in this analysis. The DMC reviewed the interim safety report on 10 July 2006 and recommended that the study continue as planned.

The second interim analysis was conducted when approximately 67% of the required deaths (280 deaths) occurred. Both safety and overall survival were assessed in this analysis. Formal comparisons between the two treatment arms of the incidence of Grade 3–5 and Grade 5 hemoptysis were made. If the incidence in the Tarceva + bevacizumab arm was unacceptable, the study would have been stopped (for the stopping guidance, see the DMC charter). The significance level for the overall survival comparison was determined using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary of 0.0124 at 67% event time and 0.0462 at the final analysis. The overall survival result was not positive, so the study was continued until 417 deaths occurred.

All summaries/analyses by treatment arm for the DMC review were performed by an independent Data Coordinating Center (DCC). The study team remained blinded to the treatment assignment until study unblinding.

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

1. BACKGROUND

1.1 INTRODUCTION

Lung cancer is the leading cause of cancer-related death in North America (Pazdur et al. 2004). Eighty percent of lung cancer is non–small cell lung cancer (NSCLC), and ~75% of patients with NSCLC present with advanced stage disease (unresectable or metastatic disease). The overall 5-year survival rate for patients who develop lung cancer in the United States is 14%, having only slightly improved over the past 20 years (DeVita et al. 2001). Patients who present with Stage IIIB and Stage IV disease have fairly equal and dismal prognoses, with 5-year survival rates of 6% to 8% (Mountain 1997). Median survival for patients with metastatic NSCLC is historically ~4 months when treated with best supportive care (Bunn et al. 1998).

Advances made in the last decade with the development of cytotoxic therapies for NSCLC have had little impact on overall survival in patients with advanced stage disease. Platinum-based doublet chemotherapy (primarily carboplatin/paclitaxel in the United States) has remained the standard front-line treatment of advanced disease, with multiple randomized trials confirming a median survival of 8 months and response rates averaging 26% (Schiller et al. 2002). Although newer chemotherapeutic agents (gemcitabine, vinorelbine, docetaxel) have been able to improve the quality of patients' lives and prolong survival (Bunn et al. 1998; Bunn and Kelly 1998; Carney 1998; Sweeney and Sandler 1998), patients will eventually become refractory to or suffer dose-limiting toxicity from cytotoxic therapy.

Therapeutic options for patients after relapse were limited to best supportive care or palliation until a trial comparing docetaxel with best supportive care showed that patients with NSCLC could benefit from second-line chemotherapy after cisplatin-based first-line regimens failed (Shepherd et al. 2000). Benefit was measured in terms of prolongation of time to disease progression and overall survival, improvement in symptoms, reduction in the need for cancer-related medicines (in particular narcotic pain medications), and improvement in several quality-of-life indices. A second trial comparing docetaxel with ifosfamide or vinorelbine confirmed that docetaxel provides a benefit, with an improvement in 1-year survival (30% vs. 20%; Fossella et al. 2000). The benefit of docetaxel monotherapy does not extend beyond second-line treatment. Patients receiving docetaxel as third-line treatment or beyond showed no prolongation of survival (Shepherd et al. 2000).

In August 2004, another cytotoxic agent, pemetrexed (Alimta®), received approval from the Food and Drug Administration (FDA) as second-line therapy for patients with advanced NSCLC. This approval was based on a randomized Phase III trial involving 571 patients that compared single-agent pemetrexed with single-agent docetaxel (Hanna et al. 2004). Although this trial did not demonstrate statistical non-inferiority vs. docetaxel with respect to efficacy, the two agents produced similar response rates and

progression-free, median, and 1-year survival. In addition, pemetrexed was associated with a lower incidence of toxicity than docetaxel.

Despite these chemotherapeutic advances, many advanced stage patients are still unable to tolerate these cytotoxic therapies, and their prognosis remains poor. Therefore, efforts are ongoing to develop effective regimens without significantly increasing toxicity. Strategies that target tumor cell growth, such as inhibiting tumor angiogenesis or targeting the cell surface receptors responsible for modulating tumor cell proliferation, have the potential to demonstrate increased target specificity and therefore, presumably, less overall toxicity. One of these agents, Tarceva® (erlotinib), is a small molecule inhibitor of the epidermal growth factor receptor (EGFR), an important receptor for signaling tumor cell proliferation. In the pivotal Phase III study BR.21, Tarceva was shown to improve overall survival in second- and third-line NSCLC patients versus placebo (Shepherd et al. 2004). Furthermore, the trial showed that Tarceva was well tolerated and associated with a longer time to symptom deterioration compared with placebo. Based on the data from this trial, in November 2004, the FDA approved Tarceva for the treatment of patients with locally advanced or metastatic NSCLC following failure of at least one prior chemotherapy regimen.

Bevacizumab, another targeted agent, is a recombinant monoclonal antibody that targets vascular endothelial growth factor (VEGF), a critical factor in tumor angiogenesis (Ferrara and Davis-Smyth 1997). Bevacizumab (Avastin®) was approved by the FDA for first- and second-line treatment of metastatic colorectal carcinoma in combination with intravenous (IV) 5-fluorouracil–based chemotherapy in February 2004 and June 2006, respectively. Bevacizumab also demonstrated encouraging activity in NSCLC in a randomized Phase II trial (AVF0757g) when administered in combination with carboplatin and paclitaxel (Johnson et al. 2004). In this study, patients receiving chemotherapy + bevacizumab had higher response rates, longer median time to progression (TTP), and a modest increase in survival. Based on these data, the Eastern Cooperative Oncology Group (ECOG) conducted a first-line Phase III trial (E4599) with carboplatin/paclitaxel ± bevacizumab in non-squamous NSCLC. The results from this trial demonstrated that the combination provided a significant improvement in overall survival (Sandler et al. 2005). (Please refer to the respective Investigator Brochures for additional information on the physical and pharmaceutical properties and a review of nonclinical studies for each agent.)

This Phase III study was designed to evaluate the combination of the aforementioned targeted agents (the anti-angiogenic agent bevacizumab plus the EGFR inhibitor Tarceva) against Tarceva alone. It was hypothesized that the potential complementary mechanisms of tumor control of these two agents, both active in NSCLC, might translate into added efficacy of the combination over single-agent Tarceva's proven clinical benefit while maintaining tolerability. In this trial, efficacy was assessed in terms of overall survival. Efficacy was also evaluated in terms of progression-free survival (PFS), objective response rate (ORR), duration of objective response, and clinical benefit.

The final analysis of the BETA lung trial was conducted in October, 2008. The trial did not demonstrate an improved overall survival for patients treated with Tarceva and bevacizumab compared with those treated with Tarceva and placebo. However, there was evidence of clinical activity evidenced by improvements in PFS and objective response (see Appendix C).

1.2 CLINICAL EXPERIENCE WITH BEVACIZUMAB

Bevacizumab has been studied in at least 3500 patients in a number of Phase I, II, and III clinical trials. These clinical trials have included patients with a number of tumor types, including colorectal, breast, lung, and renal carcinoma. The following discussion summarizes bevacizumab's safety profile and presents efficacy results pertinent to this trial. Please refer to the Avastin® Investigator Brochure or Package Insert for descriptions of all completed Phase I, II, and III trials.

In a large Phase III study (AVF2107g) of patients with metastatic colorectal cancer, the addition of bevacizumab to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio (HR) of death of 0.660 (median survival 15.6 vs. 20.3 months; $p < 0.0001$). Similar increases were seen in PFS (6.2 vs. 10.6 months; $p < 0.0001$), overall response rate (35% vs. 45%; $p < 0.0029$), and duration of response (7.1 vs. 10.4 months; $p < 0.0014$) for the combination arm versus the chemotherapy only arm (Hurwitz et al. 2004).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved by the U.S. FDA for first-line treatment in combination with IV 5-FU–based chemotherapy for patients with metastatic colorectal cancer (CRC).

The approval of bevacizumab for the second-line treatment of metastatic colorectal carcinoma was based upon results of a randomized, controlled, multicenter, Phase III trial of 829 patients with advanced or metastatic CRC who had received previous treatment with irinotecan and 5-FU as initial therapy for metastatic disease or as adjuvant therapy (Study E3200). The study showed that patients who received bevacizumab plus the 5-FU-based chemotherapy regimen known as FOLFOX4 (oxaliplatin/5-FU/leucovorin) had a 25% reduction in the risk of death (the primary endpoint; hazard ratio of 0.75 [95% CI 0.63, 0.89], $p = 0.001$ stratified logrank test), which was equivalent to a 33% improvement in overall survival, compared with patients who received FOLFOX4 alone. Median survival for patients receiving bevacizumab plus FOLFOX4 was 13.0 months, compared with 10.8 months for those receiving FOLFOX4 alone (Giantonia et al. 2005)

In October of 2006, bevacizumab was approved for the first-line treatment of non-resectable, locally advanced, or metastatic non-squamous NSCLC. This approval

was based on the results of the Eastern Cooperative Group (ECOG) Study 4599. The results of this trial are described in Section 1.2.2

In February 2008, bevacizumab given in combination with paclitaxel was approved for the first-line treatment of metastatic breast carcinoma. This approval was based on the results of the ECOG Study 2100, a Phase III trial conducted in 722 patients. In this trial, the combination of bevacizumab and paclitaxel increased PFS to 11.3 months compared to 5.8 months with paclitaxel alone (hazard ratio [HR], 0.48; P< .0001). The combination was not associated with an improvement in overall survival. The overall survival was 26.5 months with bevacizumab and paclitaxel compared to 24.8 months for paclitaxel alone (HR, 0.87; P=0.14).

1.2.1 Safety Profile

In the Phase I and II studies, four potential bevacizumab-associated safety concerns were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Completed Phase II and Phase III studies of bevacizumab have further defined the safety profile of this agent in patients with metastatic malignancies. Also during the Phase III studies, three new possible bevacizumab-associated safety concerns were identified: congestive heart failure in patients who had been exposed to anthracyclines, gastrointestinal perforations, and wound healing complications.

Hypertension: In Study AVF2107g, hypertension of any grade occurred in 22.4% of patients receiving IFL + bevacizumab compared with 8.3% receiving IFL + placebo. National Cancer Institute Common Toxicity Criteria (NCI-CTC) Grade 3 hypertension (requiring oral anti-hypertensive medication) was reported in 11.0% of patients receiving IFL + bevacizumab compared with 2.3% of patients receiving IFL + placebo. The overall incidence of hypertension adverse events in Study AVF0757g was 17.6% (5.9% Grade 3) in the 15 mg/kg/q3 wk arm vs. 3.1% in the control arm. Across clinical studies, the incidence of NCI-CTC Grade 3 or 4 hypertension ranged from 8% to 18%. Oral medications have been used to manage the hypertension when indicated. Grade 4 hypertensive events are rare; however, hypertensive encephalopathy associated with fatal outcome has been reported. In addition, reversible posterior leukoencephalopathy syndrome (RPLS) has been described in association with moderate hypertension (Glusker et al. 2006).

Proteinuria: Proteinuria, ranging from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome, has been seen in all clinical trials to date. The majority of proteinuria events have been Grade 1 or 2. In Studies AVF0757g and ECOG 3200, the incidence of NCI-CTC Grade 3 or 4 proteinuria, characterized as >3.5 gm/24 hr, ranged up to 1.8% in bevacizumab-treated patients.

Gastrointestinal perforation: Gastrointestinal perforation was not seen in the bevacizumab Phase I or II clinical trials; however, in the Phase III metastatic CRC trials, the incidence of gastrointestinal perforation, fistula formation, and/or intra-abdominal

abscess in patients receiving bevacizumab was 2.4%. These episodes occurred at various timepoints during treatment. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and emesis.

In post-marketing clinical studies and reports, gastrointestinal perforation, fistula formation and/or intra-abdominal abscess occurred in patients receiving bevacizumab for colorectal and for other types of cancer. Of the reported events, approximately 30% were fatal. Patients with gastrointestinal perforation, regardless of underlying cancer, typically presented with abdominal pain, nausea, and fever. Events were reported at various timepoints during treatment ranging from 1 week to greater than 1 year from initiation of bevacizumab, with most events occurring within the first 50 days.

Hemorrhage: In the Phase II NSCLC trial (Johnson et al. 2004), 6 of 66 bevacizumab-treated patients experienced life-threatening hemoptysis or hematemesis. Four of these events were fatal. An analysis of possible risk factors for life-threatening bleeding identified squamous cell histology (4 of 6 bleeds occurred in patients with squamous cell histology, whereas only 13 of 66 treated patients had squamous cell histology) and centrally located cavitary and/or necrotic lesions as potential risk factors.

At the ASCO Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2006, a retrospective analysis of clinical and radiographic risk factors associated with the development of pulmonary hemorrhage in bevacizumab-treated NSCLC patients was reported (Sandler et al. 2006). The authors suggested a potential association of pulmonary hemorrhage with hemoptysis and tumor cavitation. However, the number of cases was too small to make a conclusive statement.

On this basis, the enrollment of patients with squamous cell NSCLC in this trial is limited to those with lesions at low risk for life-threatening hemorrhage. Patients at low risk are defined as those with peripheral lung lesions or extrathoracic lesions. Patients with squamous histology with lesions other than peripheral are not recommended for study participation. The definition for a peripheral lung lesion is given in Section 4.1.3

Congestive heart failure: Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left ventricular dysfunction, has been reported in patients receiving bevacizumab. The risk of CHF appears to be higher in patients receiving bevacizumab who have received prior or concurrent anthracyclines. Prior radiation therapy to the chest wall may also increase the risk of CHF in these patients.

Additional safety signals: Other safety concerns seen to date—asthenia, pain, headache, fever, chills, rash, infection, epistaxis, and mouth ulceration—are not thought to be clinically significant because they rarely or never required treatment or study drug discontinuation.

Please refer to the Avastin® Investigator Brochure or Package Insert for additional details regarding safety experience with bevacizumab.

1.2.2 Efficacy Results in Non–Small Cell Lung Cancer

In a randomized, Phase II study in advanced NSCLC (Study AVF0757g) (Johnson et al. 2004), 99 patients with Stage IIIB, Stage IV, or recurrent NSCLC were randomized to receive either paclitaxel/carboplatin alone or paclitaxel/carboplatin + bevacizumab (either at 7.5 mg/kg or 15 mg/kg every 3 weeks). In that study, the best confirmed response rate was higher for the high-dose bevacizumab arm compared with the control arm (investigator assessment, 32% vs. 19%). Time to disease progression was also higher for the high-dose bevacizumab arm (investigator assessment; median 225 days vs. 129 days for the control). When patients with squamous cell NSCLC histology were excluded, the confirmed response rate, time to progression, and overall survival were higher for high-dose bevacizumab compared with the control arm. Based on these results, ECOG conducted a first-line Phase III trial with paclitaxel/carboplatin + bevacizumab in non-squamous cell NSCLC, ECOG Study 4599. An interim analysis of the data from this trial met its primary efficacy endpoint of improving overall survival, or a reduction in the risk of death, compared with chemotherapy alone. The rate of bevacizumab-related pulmonary hemorrhage in ECOG Study 4599 was 1.8% (Sandler 2005).

The Avastin® in Lung (AVAIL) trial, a Phase III trial in which 1043 patients were enrolled, supported the results of ECOG 4599 by demonstrating an improved PFS for patients randomized to receive bevacizumab at 1 of 2 doses (7.5 mg/kg or 15 mg/kg) with chemotherapy, gemcitabine, and cisplatinum, compared with chemotherapy alone. The median PFS was 6.7 months in the 7.5 mg/kg bevacizumab arm and 6.5 months in the 15 mg/kg bevacizumab arm compared with 6.1 months in the chemotherapy alone arm. The hazard ratios were 0.75 (P = .002) for the lower dose and 0.82 (P = .03) for the higher dose.

Please refer to Section 1.4 and the Avastin Investigator Brochure or Package Insert for additional details regarding the efficacy of bevacizumab in treating NSCLC.

1.3 CLINICAL EXPERIENCE WITH TARCEVA

Tarceva has been studied in at least 4000 patients in a number of Phase I, II, and III clinical trials. The following section summarizes Tarceva's safety profile and presents efficacy results pertinent to this trial. Please refer to the Tarceva® Investigator Brochure or Package Insert (see Appendix B) for descriptions of all completed Phase I, II, and III trials.

1.3.1 Safety Profile

Multiple Phase II and III trials of Tarceva have been conducted in patients with advanced, refractory malignancies. Of the 731 NSCLC patients enrolled in the second-

and third-line trial of single-agent Tarceva versus placebo, nearly 500 received Tarceva at 150 mg/day. Seventy-five percent of the patients experienced rash (8% were Grade 3 rash). Gastrointestinal events also occurred frequently; these included diarrhea (54%, of which 6% were Grade 3).

Rash: A papular, pustular rash manifesting most often on the face and upper trunk was common across all studies, but rash was rarely the cause of study drug discontinuation. The median time to onset of rash was 8 days. The rash may be associated with erythema, pain, pruritus, dryness, and less commonly, stomatitis and keratitis.

Diarrhea: Diarrhea was the dose-limiting toxicity at 200 mg/day, but it is generally mild (Grade 1 or 2) and manageable at 150 mg/day. The overall incidence of diarrhea in the Phase III study of single-agent Tarceva in NSCLC (Study BR.21) was 54%, of which 6% was Grade 3 or 4.

Rare cases of acute renal failure or renal insufficiency (including fatalities) with or without hypokalemia have been reported. Some have been secondary to severe dehydration due to diarrhea, vomiting, and/or anorexia, while others have been confounded by concurrent chemotherapy use. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration.

Interstitial lung disease: Non-fatal and fatal cases of interstitial lung disease (ILD) have been reported in association with the use of Tarceva in patients with NSCLC. The diagnosis of ILD is rarely definitive in cancer patients, who often have concurrent, confounding medical problems. However, a broad search (using 24 separate terms felt to be possibly reflective of a diagnosis of ILD) of the global safety database in April 2004 has identified 23 cases of possible ILD, irrespective of investigator-assessed causality. With at least 4000 patients previously treated with Tarceva, this represents a reporting incidence of 0.70%. Of these 23 cases, 16 have been assessed by the investigator as possibly related to study drug.

Hepatotoxicity: Cases of hepatic failure and hepatorenal syndrome, including fatalities, have been reported during use of Tarceva, particularly in patients with baseline hepatic impairment. These reports have been collected during postmarketing surveillance. The incidence appears to be rare.

Drug interactions: Tarceva is 92%–95% protein bound and metabolized by hepatic cytochromes CYP3A4 and CYP1A2 and pulmonary cytochrome CYP1A1. Therefore, a potential for drug–drug interaction exists when Tarceva is co-administered with drugs that are highly protein bound or that are CYP3A4 inhibitors or inducers. In addition to these possibilities, altered coagulation parameters have been reported in patients receiving Tarceva in combination with warfarin.

Other serious and nonserious adverse events have been reported. Details are provided in the Tarceva® Investigator Brochure and Package Insert (see Appendix B).

1.3.2 Efficacy Results in Non–Small Cell Lung Cancer

Study BR.21, an international study conducted by the NCIC-CTG, randomized previously treated patients with advanced or metastatic NSCLC in a 2:1 ratio to single-agent Tarceva at 150 mg/day versus placebo (Shepherd et al. 2004). Enrollment was completed in January 2003, with a total of 731 patients enrolled.

The trial met its primary endpoint of improving overall survival in second- and third-line NSCLC patients. Patients receiving Tarceva had a median survival of 6.7 months compared with 4.7 months for those receiving placebo (a 42.5% improvement; HR = 0.73; p = 0.001). The trial also met its secondary endpoints, including improvements in time to symptom deterioration, PFS, and ORR. The ORR was 8.9% in Tarceva-treated patients versus < 0.9% in placebo-treated patients.

Two other Phase III randomized studies in first-line NSCLC patients evaluated Tarceva in combination with platinum-based doublet chemotherapy. A total of 1059 (1079 randomized) previously untreated patients received carboplatin/paclitaxel with either Tarceva or placebo in the TRIBUTE study (OSI2298g), conducted in the United States (Herbst et al. 2004). An additional 1159 (1172 randomized) patients received cisplatin/gemcitabine plus either Tarceva or placebo in the TALENT study (BO16411), which was conducted in 27 countries in Europe and other locations outside of the United States (Gatzemeier et al. 2004). Neither study met its primary endpoint of improved overall survival or its secondary endpoints of improved time to disease progression and overall response rate.

Preliminary data suggest that patients with no prior smoking history respond particularly well to EGFR inhibitors, as assessed by both response and survival. The TRIBUTE study collected smoking history at entry. “Never-smokers” randomized to receive Tarceva with chemotherapy had a median survival of 22 months as opposed to 10 months for never-smokers in the placebo arm (Miller et al. 2004).

Analysis of the impact of EGFR expression status on the treatment effect on clinical outcome of patients receiving Tarceva is limited because EGFR status is known for only one third of patients enrolled in Study BR.21. For this study, positive EGFR expression status was defined as having ≥ 10% of cells staining for EGFR in contrast to the 1% cutoff specified in the DAKO EGFR pharmDx™ kit instructions.

Tarceva prolonged survival in the EGFR-positive subgroup (n = 185; HR = 0.68; 95% confidence interval [CI] = 0.49, 0.94) and the subgroup whose EGFR status was unmeasured (n = 405; HR = 0.77; 95% CI = 0.61, 0.98), but did not appear to have an effect on survival in the EGFR-negative subgroup (n = 141; HR = 0.93; 95% CI = 0.63, 1.36). However, the CIs for the EGFR-positive, unmeasured, and EGFR-negative

subgroups are wide and overlap, so that a survival benefit due to Tarceva in the EGFR-negative subgroup cannot be excluded. Tumor responses were observed in all EGFR subgroups: 11.3% in the EGFR-positive subgroup, 9.5% in the EGFR unmeasured group, and 3.8% in the EGFR-negative subgroup.

An improvement in PFS was demonstrated in the EGFR-positive subgroup (HR = 0.49; 95% CI = 0.35, 0.68), the EGFR unmeasured subgroup (HR = 0.60; 95% CI = 0.47, 0.75), and less certain in the EGFR-negative subgroup (HR = 0.80; 95% CI = 0.55, 1.16; US PI).

1.3.3 EGFR Mutations in Non–Small Cell Lung Cancer

The recent identification of mutations within the EGFR in the tumor tissue of a subset of patients with NSCLC and the association of these mutations with sensitivity to gefitinib (Lynch et al. 2004; Paez et al. 2004) support the hypothesis that these are activating mutations that also render the tumors sensitive to the effects of EGFR tyrosine kinase inhibitors. For the two reports pooled, mutated EGFR was observed in 13 of 14 patients who responded to gefitinib and in none of the 11 patients who were treated and did not respond. The relationship of mutation to prolonged stable disease or survival duration has not been prospectively evaluated. Patients were selectively identified for this analysis based on a rapid or dramatic response. Data from large numbers of unselected patients prospectively enrolled in clinical trials are needed to more fully understand the clinical significance of these mutations.

The association between the presence of EGFR mutations and clinical response was also seen with Tarceva, as reported in an analysis of patients enrolled in the TRIBUTE study (Eberhard et al. 2004). Of the 228 patients with available tissue, 29 had evidence of EGFR mutations, for a prevalence of 12.7%. Among these 29 patients, the 15 who received chemotherapy + Tarceva had a trend toward prolonged TTP and improved response rate compared with the 14 who received chemotherapy only ($p = 0.092$ and $p < 0.01$, respectively). Patients with EGFR-mutant tumors, irrespective of whether they received Tarceva or placebo with chemotherapy, survived longer (median survival not reached) than patients with wild-type EGFR (MS 9.6 and 11.7 months, $p < 0.001$), suggesting that EGFR mutation is a positive prognostic factor independent of EGFR inhibitor therapy.

The improved TTP and response rate have not translated into improved survival for patients with EGFR-mutant tumors receiving chemotherapy + Tarceva compared with patients receiving chemotherapy alone ($p = 0.958$). However, the number of patients with available tissue was small, and the duration of follow-up was short compared with the longer survival of all patients with EGFR mutations irrespective of treatment arm.

1.4 BEVACIZUMAB AND TARCEVA COMBINATION STUDIES

The strategy of combining therapeutic agents in cancer treatments has been successful in multiple tumor types, including NSCLC. A new series of clinical studies are now being designed and conducted to evaluate the combination of bevacizumab with Tarceva,

particularly in NSCLC and renal cell carcinoma. This approach has scientific rationale because the two agents target different pathways involved in tumor growth, and nonclinical studies in xenograft models have demonstrated that the combination of bevacizumab and Tarceva results in greater efficacy than either agent alone (data on file, provided by [redacted], Genentech, Inc.). Furthermore, because little to no overlap in toxicity profile between the two agents has been observed to date, the combination is expected to be well tolerated and may provide greater benefit than either agent alone for patients who are unable to receive cytotoxic therapy.

OSI2486s: Study OSI2486s is a recently completed investigator-sponsored Phase I/II study (OSI2486s) evaluating the combination of bevacizumab and Tarceva in patients with relapsed or refractory NSCLC of non-squamous histology (Herbst et al. 2005). The Phase I portion of the study evaluated three dose combinations to determine the tolerability and pharmacokinetic profile of each agent when combined. Patients whose disease had progressed following at least one chemotherapy regimen for Stage IIIB/IV disease were treated with 100 mg/day Tarceva + 7.5 mg/kg bevacizumab, 100 mg/day Tarceva + 15 mg/kg bevacizumab, or 150 mg/day Tarceva + 15 mg/kg bevacizumab (with bevacizumab administered every 3 weeks in all regimens). A total of 12 patients were enrolled and treated in the Phase I portion (3, 3, and 6 per cohort, respectively). No dose-limiting toxicities were observed, and the pharmacokinetic profiles of both drugs did not appear to be affected by the combination. As a consequence, the recommended Phase II dose was established as 150 mg/day Tarceva + 15 mg/kg bevacizumab every 3 weeks, and 28 additional patients were subsequently treated with these doses.

A total of 40 patients were enrolled in the Phase I and II portions, with 34 patients treated with full doses of both agents. Patient characteristics were as follows: median age 59 years (range: 36–72 years), 21 female/ 19 male, 30 patients with adenocarcinoma histology, 9 patients with no prior smoking history, 22 patients who received two or more prior regimens, and 3 patients who received four or more prior regimens. The most commonly reported adverse events were rash, diarrhea, and proteinuria. Importantly, there were no reports of hemoptysis. Preliminary data indicated no pharmacokinetic interaction between these two agents. The observed response rate was 20%, with a disease control rate (partial response and stable disease) of 85% and median overall survival of 12.6 months. Based on the data from this single-arm, Phase I/II study, the combination of bevacizumab and Tarceva is well tolerated at maximum doses.

The combination has encouraging activity, supporting a larger, controlled study to assess the efficacy and tolerability of the regimen.

OSI2950g: Study OSI2950g is a completed Genentech-sponsored, Phase II, multicenter, randomized, placebo-controlled study evaluating the efficacy (based on PFS) of combining bevacizumab with docetaxel, premetrexed, or Tarceva relative to docetaxel monotherapy in patients with previously treated advanced NSCLC. Eligible

patients have histologically confirmed non-squamous NSCLC and have experienced disease progression during or following one platinum-based regimen for advanced stage disease (Stage IIIB or IV). Additional eligibility criteria include no previous anti-angiogenesis agents or EGFR inhibitors, an ECOG performance status of 0 or 1, and no active central nervous system metastases. Patients are randomized in a 1:1:1 ratio to one of three treatment arms:

- Arm 1: docetaxel or premetrexed + placebo
- Arm 2: docetaxel or premetrexed + bevacizumab
- Arm 3: bevacizumab + Tarceva

The primary results of Study OSI2950g were presented at the ASCO Annual Meeting in 2006. The observed data favored the addition of bevacizumab to either chemotherapy or erlotinib over chemotherapy alone in the treatment of relapsed NSCLC. The authors went on to note that the trial was not powered to detect such a difference. Importantly, no new or unexpected safety signals for bevacizumab or Tarceva were noted during the trial. The toxicity profile of the bevacizumab + erlotinib combination showed a lower incidence of serious adverse events when compared with both of the chemotherapy-containing groups. The authors' final statement was a call for a definitive Phase III trial of this combination (Fehrenbacher et al. 2006).

AVF3120s: Study AVF3120s is an investigator-sponsored Phase II study currently being conducted to evaluate the combination of 10 mg/kg bevacizumab every 2 weeks + 150 mg/day Tarceva in patients with metastatic renal cell carcinoma (Hainsworth et al. 2004). Eligible patients have metastatic clear-cell renal cell carcinoma and no more than one previous systemic chemotherapy regimen. Patients are evaluated for response after 8 weeks. At that time, patients with a response or stable disease continue treatment for 12 months or until tumor progression. The preliminary efficacy data from this single-arm, Phase II study of 58 evaluable patients suggest a response rate of 25%, a 1-year PFS of 43%, and an 18-month survival of 60%. The most commonly observed toxicities include rash, diarrhea, proteinuria, and bleeding (usually Grade 1 or 2).

AVF2938g: Study AVF2938g, a Genentech-sponsored, Phase II, randomized study conducted to evaluate the combination of bevacizumab + Tarceva versus bevacizumab alone in patients with metastatic renal cell carcinoma, did not demonstrate clinical benefit for those patients receiving the bevacizumab + Tarceva combination. Similarly, there was no increase in toxicity in those patients treated with the combination (Bukowski et al. 2006).

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this Phase III study was to evaluate the efficacy of combining bevacizumab with Tarceva (erlotinib) relative to Tarceva monotherapy in patients

receiving second-line therapy for advanced NSCLC. Efficacy will be assessed by measuring overall survival.

The addition of bevacizumab to erlotinib in the BETA lung study was not associated with an improvement in overall survival. However, bevacizumab when combined with erlotinib improved PFS and ORR, demonstrating evidence of clinical activity.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this Phase III study were as follows:

- To evaluate the safety of combining bevacizumab with Tarceva in patients with previously treated advanced NSCLC, including patients with squamous cell carcinoma, patients with treated brain metastases, and patients receiving full-dose anticoagulation with low-molecular-weight heparin or fondaparinux.

  Note: See Section 4.1.2 for the eligibility criteria regarding squamous cell carcinoma patients.

  Note: Upon enactment of Amendment 6, safety data collection will be restricted to the reporting of serious adverse events via MedWatch FDA 3500 forms (Appendix D) and will not be captured in the CRF.

- To evaluate the efficacy of combining bevacizumab with Tarceva relative to Tarceva monotherapy in patients with previously treated advanced NSCLC, as measured by PFS, ORR, and duration of response
- To evaluate the pharmacokinetic behavior of Tarceva and the combination of bevacizumab with Tarceva in a subset of patients with previously treated advanced NSCLC
- To evaluate the association of survival, PFS, and treatment effect with markers of epidermal growth factor receptor (EGFR) expression, as measured by immunohistochemistry (IHC), EGFR gene copy number measured by fluorescence in situ hybridization (FISH), and other molecular markers of EGFR pathway activity in archival tissue samples

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, placebo-controlled, double-blind, randomized study. Six hundred thirty-six patients were randomized in a 1:1 ratio to one of two treatment arms:

- Arm 1: Tarceva + placebo
- Arm 2: Tarceva + bevacizumab

Treatment assignment to study drug (bevacizumab or placebo) was blinded for Genentech, the investigator, and the patient. All patients had to have cytologically or histologically confirmed NSCLC and had to consent to allow analysis of their archival

diagnostic tissue, if available. For safety reasons, patients with squamous cell histology were allowed to enroll only if they had limited disease that placed them at low risk for life-threatening hemorrhage. Their lung lesions had to be peripheral or their disease extrathoracic. Patients with brain metastases were allowed to enroll only if their brain metastases had been previously treated and they are not receiving dexamethasone.

Furthermore, all patients must have experienced disease progression (clinical or radiographic progression, as assessed by the investigator) during or following standard first-line chemotherapy or chemoradiotherapy for NSCLC. (Note: Patients receiving neo-adjuvant and adjuvant therapy for Stage I–IIIA disease prior to their first-line regimen were eligible for study participation provided they also received first-line therapy [for unresectable, metastatic disease] and demonstrated progression during or after that first-line therapy.)

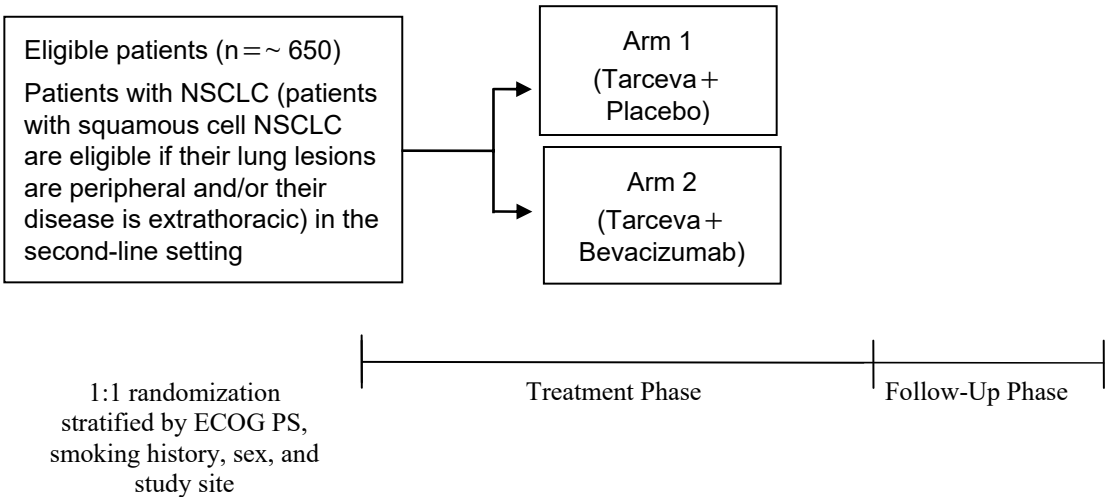
Patients were allowed to remain in the treatment phase of the study until documented radiographic or clinical disease progression, or until unmanageable toxicity (in the latter case and if the causal drug is bevacizumab/placebo, Tarceva may be continued until documented disease progression or unmanageable toxicity). Patients have been followed for survival until death, loss to follow-up, or study termination by Genentech.

A data monitoring committee (DMC) periodically reviewed safety data for all patients, for patients with brain metastases treated prior to enrollment, and for patients with squamous cell carcinoma throughout the study, including monthly serious adverse event reviews. This function was carried out by the Genentech Medical Monitor after November 2008.

Two interim analyses were conducted during the study. The first was conducted after 123 patients had been enrolled and followed for at least 2 months. Only safety data were assessed in this analysis. The DMC reviewed the interim safety report on 10 July 2006 and recommended that the study continue as planned. The second interim analysis was conducted when approximately 67% of the required deaths (280 deaths) occurred. Both safety and overall survival were assessed in this analysis. The DMC reviewed the interim report on 7 February 2008 and recommended that the study continue as planned. The final analysis was conducted in October 2008 and the results presented publicly in November 2008. See Appendix C.

The study is represented schematically in Figure 1 . Study assessments and procedures are detailed in Section 4.5 and Appendix A .

Figure 1 Study Schema



3.2 RATIONALE FOR STUDY DESIGN

The rationale for this study design is based on a hypothesis that combining bevacizumab with Tarceva should result in improved efficacy compared with Tarceva monotherapy in the setting of advanced NSCLC after failure of standard first-line chemotherapy. The proposed design included a placebo for bevacizumab in order to eliminate reporting and ascertainment bias in the final data analysis. The primary objective of this study was overall survival.

The control arm of Tarceva alone is FDA approved for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen, based on data from Study BR.21 (see Section 1.3 or Shepherd et al. 2004). Based on data from Study OSI2486s (see Section 1.4 or Herbst et al. 2005), it was hypothesized that the combination treatment arm would be well tolerated and provide greater benefit than Tarceva alone. Intensive pharmacokinetic analyses were performed in this study to evaluate the pharmacokinetic behavior of Tarceva and of the combination of the two agents.

Tumor biopsy material from patients enrolled in this study was requested in order to measure selected markers of EGFR and/or VEGF pathway activity that are thought to play an important role in clinical outcome.

Study OSI3364g did not include a chemotherapy arm, as the comparison of chemotherapy versus Tarceva in the treatment of second-line NSCLC is being addressed in other clinical trials.

3.3 OUTCOME MEASURES

3.3.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study was overall survival, defined as the period from the date of randomization until the date of patient death from any cause.

The addition of bevacizumab to erlotinib in the BETA lung study was not associated with an improvement in overall survival. However, bevacizumab when combined with erlotinib improved PFS and ORR, demonstrating evidence of clinical activity. See Appendix C.

3.3.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures were as follows:

- PFS, defined as the time from randomization to documented disease progression, as determined by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST), or death on study treatment, whichever occurs first
- Objective response, as determined by the investigator using RECIST
- Duration of objective response, defined as the period from the date of initial partial or complete response (as determined by the investigator using RECIST) until the date of disease progression or death from any cause on study treatment
- Evaluation of the relationship between molecular exploratory markers and efficacy outcomes

3.3.3 Pharmacokinetic Outcome Measures

The pharmacokinetic outcome measures for erlotinib and its metabolite (OSI-420) were as follows:

- Maximum concentration at steady state ($C_{max,ss}$)
- Time of the maximum concentration at steady state ($T_{max,ss}$)
- Minimum concentration at steady state ($C_{min,ss}$)
- Apparent clearance at steady state
- Area under the erlotinib time–concentration curve (AUC_{0-tau})

The pharmacokinetic outcome measures for bevacizumab were as follows:

- Maximum concentration (C_{max})
- Minimum concentration (C_{min})

3.3.4 Safety Outcome Measures

The safety outcome measures for this study were the following:

- Incidence and severity of adverse events and serious adverse events
- Changes in laboratory values

Patient safety after Amendment 6 will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

3.4 SAFETY PLAN

Upon enactment of Amendment 6, data collection will be restricted to reporting of serious adverse events via MedWatch FDA 3500 forms (not in the CRF), and handled according to instructions in Section 5.4. SAE data will be collected via the safety database only. Prior to Amendment 6, the safety plan was as below.

See Section 4.3.4 and Section 5 for complete details of the safety evaluation for this study.

A number of measures have been taken to ensure the safety of patients participating in this study. These measures were addressed through the exclusion criteria (see Section 4.1.3) and routine monitoring as follows.

Patients enrolled in this study were evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations consisting of medical interviews, recording of concomitant medications and adverse events, physical examinations, blood pressure, and laboratory measurements (performed by local laboratories, see Section 4.5 and Appendix A) have been conducted. Patients have been evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit while on study drug. Patients discontinued from the treatment phase of the study for any reason were evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 4.5.3). Patients with an ongoing Grade 4 or serious adverse event at the time of discontinuation from study treatment were followed until the event is resolved or determined to be irreversible by the investigator (see Section 4.5.3).

Specific monitoring procedures were as follows:

- Hypertension was monitored through routine evaluation of blood pressure.
- In patients with bleeding, a hemostasis evaluation was performed as clinically indicated. In patients with hemoptysis, bevacizumab should be permanently discontinued and protocol guidelines followed (see Section 4.3.4 and Table 2). Early use of bronchoscopy to identify the site of bleeding should also be considered.
- Patients with a history of brain metastases were monitored for the development of symptomatic Grade $\geq$ 2 CNS hemorrhage (NCI CTCAE, Version 3.0). Symptomatic is defined as clinical symptoms that are determined by the investigator to be directly referable to a CNS hemorrhage. Bevacizumab should be discontinued and protocol guidelines followed in patients who develop symptomatic Grade $\geq$ 2 CNS hemorrhage (see Section 4.3.4 and Table 2).

- Patients requiring full-dose anticoagulation could be treated with low-molecular-weight heparin or fondaparinux; these patients were and have been monitored for Grade ≥ 3 hemorrhage events. Full-dose anticoagulation with warfarin is prohibited; however, prophylactic doses were allowable.
- Bevacizumab should be discontinued and protocol guidelines followed in patients who develop symptomatic Grade ≥ 2 CNS hemorrhage or Grade ≥ 3 hemorrhage (see Section 4.3.4 and Table 2).
- Because of the potential for drug–drug interaction between Tarceva and warfarin, patients who received concomitant prophylactic/low-dose warfarin therapy were to be monitored closely for INR changes or bleeding.
- Chronic use of full-dose nonsteroidal anti-inflammatory drugs (NSAIDs) was not allowed while on study treatment. If required, the patient must be discontinued from bevacizumab/placebo.
- Aspirin up to, but not exceeding, 325 mg per day could be given to patients at high risk for arterial thromboembolic disease. Patients developing signs or symptoms of arterial thromboembolic events (see Table 2) while on study treatment were asked to discontinue bevacizumab/placebo.
- Proteinuria was monitored through regular urinalysis and urinary protein to creatinine ratio. Screening for proteinuria at ex-U.S. sites was performed with a urine dipstick (patients found to have ≥ 3+ proteinuria by dipstick had to undergo a 24-hour urine collection)
- Symptoms consistent with ILD, such as new onset dyspnea, cough, or fever without an obvious cause were to be evaluated. In the event that ILD was suspected, study treatment was to be discontinued and the patient given appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often provided. Tarceva should not be restarted in patients suspected of having drug-related ILD.
- NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving Tarceva therapy. Patients were asked to seek medical advice promptly if they experienced eye irritation during Tarceva therapy.

See Section 4.3.4 for detailed instructions about the management of study drug-related toxicities. The DMC monitored the safety of this study by reviewing serious adverse events every month and during the two interim analyses. Members of the DMC were external to Genentech and followed a charter that outlines the Committee's composition and the members' roles and responsibilities.

3.5 CONTROL GROUP

The control group consisted of patients receiving Tarceva in combination with placebo (Arm 1).

3.6 MINIMIZATION OF BIAS

To reduce bias, patients were randomized to two treatment arms (Tarceva + placebo and Tarceva + bevacizumab) using an interactive voice response system (IVRS). Genentech, the investigator, and the patient was blinded to treatment assignment of bevacizumab versus placebo.

3.7 ETHICAL CONSIDERATIONS

The prognosis for patients with previously treated advanced NSCLC is poor, with a median survival of ~4 months among untreated patients (Bunn et al. 1998). Single-agent Tarceva showed a significant survival benefit in Study BR.21 (Shepherd et al. 2004); therefore, patients receiving Tarceva + placebo will receive an FDA-approved treatment with proven efficacy in this setting.

A quality-of-life assessment using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the lung cancer module QLQ-LC13 tools was an integral part of Study BR.21. Patients treated with Tarceva monotherapy had a significantly longer time to symptom deterioration, cough, dyspnea, and pain compared with patients receiving placebo.

A survival benefit for bevacizumab in the front-line treatment of non-squamous cell NSCLC was demonstrated in ECOG Study 4599 (Sandler et al. 2005). A Phase I/II investigator-sponsored study of Tarceva + bevacizumab in non–squamous cell NSCLC (Herbst et al. 2005) and preliminary results from Study OSI2950g (Fehrenbacher et al. 2006) suggest that this benefit may extend to patients treated in the second-line setting.

Study OSI3364g was designed to test the hypothesis that the addition of bevacizumab increases the survival benefit of Tarceva.

In the Phase II NSCLC trial, AVF0757g, 6 of the 66 bevacizumab-treated patients experienced life-threatening hemoptysis or hematemesis (Johnson et al. 2004). Four of these events were fatal. Of these patients, 4 had squamous cell histology. This corresponded to a 31% rate of hemorrhage (4 of 13 patients) in patients with squamous cell disease.

A case-control evaluation performed to determine which clinical and/or radiographic factors contributed to these events concluded that squamous cell histology and bevacizumab treatment were the principal risk factors for major pulmonary hemorrhage (Novotny et al. 2001).

In Study E4599 (the Phase III trial of bevacizumab in first-line NSCLC patients), excluding those with predominant squamous histology, 10 of 427 patients (2.3%) in the bevacizumab + chemotherapy arm experienced Grade 3–5 pulmonary hemorrhage compared with 2 of 441 patients (0.5%) in the chemotherapy-alone arm.

Five of the 10 events in the bevacizumab + chemotherapy arm occurred within 9 weeks of treatment initiation. The remaining events occurred at Week 15 or later. The two events occurring in the chemotherapy-alone arm occurred at Week 16 or later. A retrospective analysis of pulmonary hemorrhage cases from Studies E4599 and AVF0757g did not conclusively identify clinical or radiographic criteria associated with an increased risk for severe pulmonary hemorrhage. Hemoptysis and tumor cavitation were felt to be potentially associated.

Based on the case-control analysis from Study AVF0757g, squamous NSCLC was the principal risk factor for severe pulmonary hemorrhage. Patients with squamous NSCLC have been excluded from subsequent clinical trials with bevacizumab, thus limiting clinical experience in this setting.

Of the 145,000 patients diagnosed with NSCLC annually, 20%–30% will have squamous cell histology. Treatment of these patients remains an area of significant unmet need (Fraire 1996; Hammar 1993; Linnoila and Aisner 1995).

The risk for pulmonary hemorrhage in patients with squamous cell NSCLC, demonstrated in Study AVF0757g, may not be uniform. Nine of the 13 patients with squamous cell history enrolled did not bleed, suggesting that it may be possible to identify a subset of patients with squamous cell histology at lower risk for hemorrhage when treated with bevacizumab.

The squamous cell NSCLC population anticipated to have the lowest risk for severe or life-threatening pulmonary bleeding has extra-thoracic disease (i.e., liver, adrenal, bone) and/or small volume disease in the peripheral lung parenchyma. Restriction of treatment to this population may mitigate against severe bleeding and broaden the availability of a potentially effective, well-tolerated therapy, bevacizumab combined with Tarceva, to patients with unmet medical need.

Of patients with NSCLC, 25%–30% will develop brain metastases during the course of their disease (Langer 2005). Patients with brain metastases will comprise an increasingly large proportion of the NSCLC population as patients live longer as the result of more effective therapies (Gaspar et al. 2005).

Patients with brain metastases were previously excluded from receiving bevacizumab because of the potential risk of bleeding.

In ECOG Study 4599, patients with brain metastases were ineligible for study participation; however, 38 of the 878 enrolled patients, 19 in each treatment group, developed brain metastases during the trial. Two of the 19 patients in the bevacizumab group had non-fatal bleeding events. No bleeding events were noted in the other treatment group.

The spontaneous bleeding rate of 10% in bevacizumab-treated patients is similar to the incidence of spontaneous hemorrhage reported in patients with brain metastases of various tumor types, ranging from 0.8% to 14% (Mandybur 1997; Bitoh et al. 1984). This rate drops to as low as 0%–1.2% in series of patients treated with whole brain radiotherapy (WBRT), stereotactic radiosurgery, and surgery (Andrews et al. 2004; Noel et al. 2003; Maor et al. 2000). This suggests a lower spontaneous hemorrhage rate in patients with treated brain metastases.

The prognosis for patients with advanced or recurrent NSCLC is poor; the treatment options and the ability of patients to tolerate second- and third-line therapies are limited. Study OSI3364g was designed to investigate the role of Tarceva with or without bevacizumab in the setting of second-line treatment of NSCLC in an attempt to develop an effective second-line therapy without significant associated toxicity. The study has been amended to include the enrollment of patients with squamous cell carcinoma at low risk for pulmonary hemorrhage and patients with treated brain metastases (except those who have an ongoing requirement for treatment with dexamethasone at screening) to address the unmet medical need of a larger population of patients.

Patient safety continues to be of principal concern in Study OSI3364g given the novelty of the combination and the demonstrated risk for hemorrhage with bevacizumab therapy. Frequent safety monitoring of the treated population during the treatment period by a DMC is a component of this study. The DMC reviewed serious adverse events monthly and full safety data until the final analysis. They had the ability to recommend study continuance based upon their findings (see Section 4.8.8). Special attention was paid to hemorrhage events.

Genentech *performed* safety reviews after the final analysis.

The final analysis of OSI3364g showed that the addition of bevacizumab to erlotinib improved PFS and ORR. However, this clinical benefit was not associated with an improvement in survival.

Amendment 5 *allowed* investigators and patients who *had* not progressed the option to continue active study treatment until disease progression, while continuing to provide long-term data on the safety of the bevacizumab and erlotinib combination.

Forty-eight patients remained on study treatment at the time of the final BETA analysis. Some had been on study for more than 1 year. The continued collection of safety information on these long-term non-progressing patients *allowed* for a better description of the long-term safety profile of the bevacizumab and erlotinib combination.

All placebo treatment in the BETA trial will be discontinued to remove the risks and discomforts associated with infusion therapy.

Investigators and patients are not obligated to remain on study treatment. They may choose to discontinue trial participation given the failure of the study to meet its primary endpoint of improved overall survival.

Upon enactment of Amendment 6, data collection will be restricted to spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms (not in the case report form [CRF]), and handled according to instructions in Section 5.4. SAE data will be collected via the safety database only.

3.8 ADMINISTRATIVE STRUCTURE

This study has been sponsored by Genentech and managed with the support of a contract research organization (CRO) that provided clinical data management and monitoring support. Six hundred thirty-six patients were enrolled at approximately 200 centers in the United States, Europe, and the rest of the world. Randomization occurred through the IVRS (see Section 4.2).

3.9 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted according to the International Conference on Harmonisation E6 Guideline for Good Clinical Practice (GCP) and any national requirements.

4. MATERIALS AND METHODS

The materials and methods below were utilized prior to the final analysis of OSI3364g. These should be continued for all patients who remain on study treatment after the final analysis, unless stated otherwise.

4.1 PATIENTS

4.1.1 Patient Selection

Enrollment in the BETA lung trial has been completed.

Patients were eligible for this second-line therapy study if they had recurrent or refractory (progression through at least two cycles of a given chemotherapeutic regimen) NSCLC following standard first-line chemotherapy or chemoradiotherapy. This guideline was based on a number of the life-threatening and fatal hemorrhagic events in NSCLC patients, which were associated with these characteristics. This was incorporated as a guideline for this study because it is difficult to objectively quantify. Additional specific inclusion and exclusion criteria are listed below.

4.1.2 Inclusion Criteria

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

- Signed written informed consent

- Cytologically or histologically confirmed NSCLC

  Patients had to have histologically or cytologically confirmed NSCLC. Tumors of mixed histology were categorized by the predominant cell type unless small cell elements were present, in which case the patient was not eligible for study participation. Cytologic or histologic elements may have been established on metastatic tumor aspirates or biopsy.

  Patients with squamous cell carcinoma were eligible provided that their disease was extrathoracic or that their intrathoracic disease consists of peripheral lesions only. A peripheral lesion was defined as a lesion (or lesions) in which the epicenter of the tumor was $\leq$ 2 cm from the costal or diaphragmatic pleura in a 3-dimensional orientation based on each lobe of the lung, and $>$ 2 cm from the trachea, main, and lobar bronchi.

  Squamous cell carcinoma patients were eligible for study participation irrespective of the proximity of their adenopathy to the costal or diaphragmatic pleura or major airways. Patients with hilar adenopathy were eligible for study participation.

  Patients with squamous cell carcinoma had to have a copy of the screening computed tomography (CT) or magnetic resonance imaging (MRI) scans (either as copy films or digital images) reviewed by Genentech or its designee prior to randomization. Patients were not randomized until Genentech or its designee confirmed eligibility.

  Patients with a history of brain metastases were eligible for study participation, as long as their brain metastases had been treated and they did not have an ongoing requirement for treatment with dexamethasone at screening. Treatment had to be with WBRT (e.g., 3000 cGy over 2 weeks) and might include neurosurgery, or stereotactic radiosurgery. Radiotherapy and stereotactic radiosurgery had been completed at least 4 weeks prior to Day 0 (see Section 4.3.2). Neurosurgery had be completed at least 24 weeks prior to Day 0, and brain biopsy must be completed at least 12 weeks prior to Day 0.

- Clinical or radiographic progression during or after first-line chemotherapy or chemoradiotherapy for NSCLC

  Patients receiving neo-adjuvant and adjuvant therapy for Stage I–IIIa disease prior to their first-line regimen were eligible for study participation provided they had also received first-line therapy (for unresectable, metastatic disease) and had demonstrated progression during or after that first-line therapy.

- Consent to provide archival tissue for analysis was required for participation in this study. Patients who consented to provide tissue but whose archival tissue was found to be inadequate (e.g., stained slides) remained eligible for study participation).
- ECOG performance status of 0, 1, or 2
- Age $\geq$ 18 years

- Use of an acceptable means of contraception for men and women of childbearing potential
- INR no greater than 1.3 and an aPTT no greater than the upper limits of normal within 28 days prior to enrollment for patients not on low-molecular-weight heparin or fondaparinux. Patients on low-molecular-weight heparin or fondaparinux were not required to meet INR or aPTT limits.

4.1.3 Exclusion Criteria

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

- Squamous cell carcinoma, except for patients with no intrathoracic disease or small peripheral lesions only

  A peripheral lung lesion was defined as any lesion meeting the following criteria: A lesion (or lesions) in which the epicenter of the tumor was $\leq$ 2 cm from the costal or diaphragmatic pleura in a 3-dimensional orientation based on each lobe of the lung, and $>$ 2 cm from the trachea, main, and lobar bronchi.

  Adenopathy was not considered when assessing the peripheral nature of a patient's squamous cell carcinoma. Patients were eligible for study participation irrespective of the proximity of their adenopathy to the costal or diaphragmatic pleura or major airways.
- Prior treatment with an investigational or marketed inhibitor of the EGFR pathway or anti-angiogenesis agent

  Angiogenesis inhibitors include (but are not limited to) bevacizumab, thalidomide, CP 547632, SU 11248, and PTK 787.
- Systemic chemotherapy, radiotherapy, or investigational treatment within 28 days prior to randomization
- Local palliative radiotherapy within 14 days prior to randomization or persistent adverse effects from radiotherapy that have not resolved to Grade 2 or less following completion of treatment
- Whole brain radiotherapy or stereotactic radiosurgery for brain metastases within 4 weeks of Day 0 (see Section 4.3.2)
- Neurosurgery for brain metastases within 24 weeks of Day 0 (see Section 4.3.2)
- Brain biopsy within 12 weeks of Day 0 (see Section 4.3.2)
- Current use of dexamethasone for treatment associated with brain metastases
- History of gross hemoptysis (defined as bright red blood of at least 1/2 teaspoon or 2.5 mL per episode) within 3 months prior to randomization unless definitively treated with surgery or radiation

- History of any of the following within 6 months prior to Day 0: serious systemic disease, including myocardial infarction, uncontrolled hypertension (systolic blood pressure $>$150 mm Hg or diastolic blood pressure $>$100 mm Hg taken per the JNC 7 guidelines [see http://www.nhlbi.nih.gov/guidelines/hypertension/jncintro.htm]), unstable angina, New York Heart Association (NYHA) Grade 2 or greater CHF, unstable symptomatic arrhythmia requiring medication (patients with chronic atrial arrhythmia, i.e., atrial fibrillation or paroxysmal supraventricular tachycardia are eligible), clinically significant peripheral vascular disease, abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess

  Patients with evidence of hypertension during study screening were to be evaluated for uncontrolled hypertension in accordance with the JNC 7 guidelines.
- Evidence of bleeding diathesis or coagulopathy or other serious or acute internal bleeding within 6 months prior to randomization
- CNS bleeding; history or clinical evidence of CNS stroke (hemorrhagic or thrombotic) within the last 6 months
- Progressive neurologic symptoms in patients with a history of brain metastases
- Full-dose anticoagulation with warfarin

  Patients who required full-dose anticoagulation could be treated with low-molecular-weight heparin or fondaparinux. Patients fully anticoagulated with warfarin during the study were discontinued from bevacizumab/placebo.
- Chronic daily use of aspirin ($>$325 mg/day) or other full-dose NSAIDs with anti-platelet activity

  Treatment with other antiplatelet agents (e.g., dipyridamole, ticlopidine, clopidogrel, and/or cilostazol) was permitted.
- In-patient surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization (placement of a central line is not considered surgery, and could be placed on the same day as study drug administration)
- Minor surgical procedure, fine needle aspirations or core biopsy within 7 days prior to randomization
- Anticipation of need for a major surgical procedure during the course of the study
- Serious, non-healing wound, ulcer, or bone fracture
- Inability to take oral medication or requirement for IV alimentation or total parenteral nutrition with lipids, or prior surgical procedures affecting absorption
- Any of the following abnormal hematologic values (within 1 week prior to randomization)

  ANC $\leq$ 1000 cells/μL

  Platelet count $\leq$ 100,000 cells/μL

  Hemoglobin $\leq$ 9.0 g/dL

  INR $\geq$ 1.5 $\times$ upper limit of normal (ULN)

- Any of the following abnormal liver function tests (within 1 week prior to randomization)

  Serum bilirubin ≥ 1.5 × ULN

  Albumin ≤ 2.5 g/dL

  Serum ALT ≥ 2 × ULN (unless clearly due to liver metastases, then 5 × ULN)

  Serum AST ≥ 2 × ULN (unless clearly due to liver metastases, then 5 × ULN)

- Other baseline laboratory values

  Uncontrolled hypercalcemia (≥ 11.5 mg/dL)

  Urinary protein/creatinine ratio ≥ 1 (spot urine)

  Serum creatinine ≥ 2.0 × ULN

- Pregnancy or breast-feeding

  Because of the possible teratogenic effect, pregnant women and women who are currently breast-feeding may not participate in this study. All women of childbearing potential must have a negative pregnancy test within 1 week prior to randomization.

- Presence of another invasive cancer within 5 years prior to randomization, except for adequately treated basal or squamous cell skin cancer, or carcinoma in situ of the cervix

- Evidence of confusion or disorientation, or history of major psychiatric illness that may impair the patient's understanding of the Informed Consent Form or their ability to comply with study requirements

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Note: This study has been fully recruited and all subjects were unblinded to study drug following the final analysis. Upon enactment of Amendment 6, the interactive voice response system (IVRS) will be cancelled. Prior to enactment of Amendment 6, treatment assignment and unblinding were managed as below.

After written informed consent was obtained and eligibility established (with archival tissue identified and available for research testing), the study site obtained the patient's identification number and treatment assignment from the IVRS. Patients could be randomized up to 5 days prior to receiving their first dose of study treatment. A hierarchical dynamic randomization scheme was used to ensure an approximately equal sample size for the two treatment arms overall, within each of the four categories defined by baseline ECOG performance status (0/1 vs. 2) and smoking history (never vs. current/previous), within each sex, and within each study site.

Genentech, the investigator, and the patient were blinded to treatment assignment. Unblinding of treatment assignment prior to final study analysis was permitted only for a serious study drug–related toxicity. All cases of safety unblinding required the approval

of the Medical Monitor. After the final analysis, unblinding information was provided to all sites with patients receiving study treatment. Unblinding information for patients who had completed study treatment prior to the final analysis was provided upon request.

If a patient discontinued Tarceva therapy because of unmanageable toxicity, an unblinding request could be made to determine the treatment assignment. Study bevacizumab/placebo was discontinued and subsequent therapy provided at the discretion of the treating clinician.

Any toxicities associated or possibly associated with bevacizumab treatment were and should be managed according to standard medical practice. Discontinuation of bevacizumab has no immediate therapeutic effect. Bevacizumab has a terminal half-life of 2–3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab. Investigators were allowed to hold administration of study drug while waiting for a decision on unblinding to be made.

Any toxicities associated or possibly associated with Tarceva treatment were and should be managed according to standard medical practice. Erlotinib has a median terminal half-life of 36 hours. There is no available antidote for Tarceva.

4.3 STUDY TREATMENT

4.3.1 Formulation

a. Bevacizumab and Bevacizumab Placebo

Bevacizumab is supplied by Genentech, Inc. as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 100-mg (25 mg/mL) glass vial contains bevacizumab with a vehicle consisting of sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are for single use only. For further details, see the Avastin® Investigator Brochure or Package Insert.

Placebo consisted of vehicle for bevacizumab without the antibody.
Placebo was supplied by Genentech as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each glass vial contains sodium phosphate, trehalose, polysorbate 20, and SWFI, USP. Vials contain no preservatives and were for single use only.

Placebo treatment was discontinued as of 15 November 2008 on a case-by-case scenario. All placebo treatment will be discontinued as of the enactment of Protocol Amendment 5.

b. Tarceva

Tarceva will be supplied by Astellas Pharmaceuticals US on behalf of OSI Pharmaceuticals LLC, Inc. and F. Hoffmann-La Roche, Ltd. The oral tablets are conventional, immediate-release tablets containing erlotinib as hydrochloride salt. In

addition to the active ingredient (erlotinib), tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, magnesium stearate, and the film coating Opadry® White, which is composed of hypromellose, hydroxypropyl cellulose, and titanium dioxide. Tablets containing 25 mg, 100 mg, and 150 mg of Tarceva are available. *Erlotinib will be provided in a bottle.* Each bottle *will contain* 30 tablets, a quantity sufficient for 4 consecutive weeks of dosing, with overage. For further details, see the Tarceva® Investigator Brochure or Package Insert (see Appendix B).

4.3.2 Dosage, Administration, and Storage

a. Bevacizumab/Placebo

The dose of bevacizumab in this study continues to be 15 mg/kg administered by IV infusion on the first day of each 3-week cycle (± 4 days; the interval between infusions must not be < 17 days). The bevacizumab dose should be based on the patient's weight at screening (within 7 days prior to randomization) and should remain the same throughout the study (± 5% dosing variation). If bevacizumab/placebo administration fell outside of the 4-day visit window, for reasons other than toxicity management, the site had to obtain a protocol waiver prior to the infusion. The patient's schedule was then adjusted so that the subsequent bevacizumab/placebo infusion was given 3 weeks after the re-scheduled infusion.

Protocol waivers are no longer required for changes in treatment. Changes in the treatment dose or schedule may be made based upon the investigator's judgment and the institutional guidelines of the site. Placebo dosing will be discontinued for all patients on the Tarceva and placebo arm of the trial without evidence of progression as of the enactment of BETA lung trial Amendment 5.

The initial bevacizumab/placebo dose was delivered over 90 (± 10) minutes as a continuous IV infusion on Day 0. If a patient experienced an infusion-associated adverse event, he or she could be pre-medicated for the next study drug infusion; however, the infusion time could not be decreased for the subsequent infusion. If the first infusion was tolerated without infusion-associated adverse events, the second infusion could be delivered over 60 minutes (± 10 minutes). If a patient experienced infusion-associated adverse events with the 60-minute infusion, all subsequent doses were to be given over 90 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions could be delivered over 30 ± 10 minutes. If a patient experienced infusion-associated adverse events with the 30-minute infusion, all subsequent doses were to be given over 60 minutes. If the patient continued to experience infusion-associated adverse events with the 90-minute infusion, the patient's symptoms were managed per institutional standard of care.

At sites where study treatment continues, upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until use. DO NOT FREEZE. DO NOT SHAKE.

VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient.

The final analysis for Study OSI 3364g was completed in October 2008. The addition of bevacizumab to erlotinib in the study was not associated with an improvement in overall survival. However, bevacizumab when combined with erlotinib doubled PFS and ORR, providing clear evidence of clinical activity (see Appendix C). Patients' treatment assignments have subsequently been unblinded.

Investigators and their patients have the option to continue active study treatment until the time of progression, while continuing to provide long-term data on the safety of the bevacizumab and erlotinib combination. Investigators and patients may also choose to discontinue active therapy, given the failure of the study to meet the primary endpoint of improved overall survival.

In cases where the decision is made to continue study treatment, all placebo treatment will be discontinued, thus removing the risks and discomforts associated with infusion therapy. All treatment modifications should be made using the investigator's judgment and taking into account the guidance provided by the protocol, the Package Insert, and Investigator's Brochure.

b. Tarceva

The dose of Tarceva continues to be 150 mg/day orally. Tablets should be taken at the same time each day with ~200 mL (6–8 ounces) of water on an empty stomach at least 1 hour before or 2 hours after a meal. Toxicity due to Tarceva administration may be managed by symptomatic treatment, dose interruptions, and/or adjustment of the Tarceva dose (see Section 4.3.4 and Table 1).

Patient compliance in taking the assigned Tarceva daily dose was assessed by standard tablet counts. Bottles or blister packs containing the daily dose of Tarceva for 30 days were given to patients on the first day of each 3-week cycle. Previously distributed bottles or blister packs were returned to the clinic and counted; discrepancies were resolved with the patient at each clinic visit and documented in the patient's medical chart.

These drug accountability measures should be continued at sites where patients continue to receive study drug.

Tarceva tablets will be supplied for patients who have not progressed on study treatment in white, high-density polyethylene (HDPE) bottles with child-resistant closures or in PVC

blister packs sealed with aluminum foil. Bottles and blister packs should be stored at temperatures between 15°C and 30°C (59°F and 86°F).

4.3.3 Dosage Modification

Upon enactment of Amendment 6, no dose adjustments will be permitted. Any patient requiring a dose modification due to an AE or PD should be terminated from the study and treated following the physician's usual standard of care. Prior to Amendment 6, dose modifications were handled as below.

a. Bevacizumab/Placebo

Patients should continue to be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab/placebo, treatment with bevacizumab/placebo should be discontinued. All placebo treatment will be discontinued as of the enactment of Amendment 5.

Patients have the option to continue on single-agent Tarceva until disease progression or unmanageable Tarceva toxicity.

Infusion Reaction. Infusion of bevacizumab/placebo should be interrupted for patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0) Grade 3 or 4 allergic reaction/hypersensitivity, acute respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab/placebo treatment.

The infusion should be slowed to 50% or less or interrupted for patients who experience any infusion-associated symptoms not specified above. When the patient's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. See Section 4.2 for the study drug unblinding procedure.

b. Tarceva

Dose reduction or interruption of Tarceva for toxicity may take place at any time during the study. Dose level reductions are presented in Table 1. If patients do not tolerate the second dose reduction, they should be withdrawn from Tarceva treatment and the treatment phase of the study and should enter survival follow-up. If a patient was discontinued because of Tarceva toxicity, prior to Amendment 5, an unblinding request could be made by the investigator to determine the treatment assignment. The treatment assignments of the patients remaining on trial have been unblinded to their clinical team. Subsequent therapy will be provided at the discretion of the treating clinician.

Table 1 Tarceva Dose Level Reductions

Starting Dose	First Reduction	Second Reduction
150 mg/day	100 mg/day	50 mg/day

4.3.4 Management of Toxicities Related to Study Treatment

Upon enactment of Amendment 6, no dose adjustments will be permitted. Any patient requiring a dose modification due to an AE or PD should be terminated from the study and treated following the physician's usual standard of care. Prior to Amendment 6, toxicities related to study treatment were managed were handled as below.

Criteria for dose modification and guidelines for the management of toxicities are summarized in Table 2 .

These criteria should be followed for all patients who remain on study treatment after the enactment of Amendment 5. However, all treatment decisions are to be made by the treating physician based on his or her clinical judgment and in accordance with institutional practice and guidelines.

Table 2 Dosage Modification Criteria and Guidelines for Management of Study Treatment–Related Toxicities

NCI CTCAE Grade	Study Drug Dose Modification	Guideline for Management
Diarrhea		
Grade 1	None.	Consider loperamide (4 mg at first onset, followed by 2 mg every 2–4 hours until the patient is diarrhea-free for 12 hours).
Grade 2	None. (Dose reduction of Tarceva is necessary if diarrhea persists over 48–72 hours despite optimal medical management.)	Loperamide (4 mg at first onset, followed by 2 mg every 2–4 hours until the patient is diarrhea-free for 12 hours).
Grade 3	Interrupt Tarceva until resolution to Grade ≤ 1, and restart at next reduced dose. Continue bevacizumab/placebo.	Per standard of care practices.
Grade 4	Discontinue the patient from Tarceva and the study treatment phase of the study, including permanent discontinuation of bevacizumab/placebo.	As listed above.
Hemorrhage [a]		
Grade 1 pulmonary	Hold bevacizumab/placebo and evaluate source. Continue Tarceva.	In patients with hemoptysis, consider early use of bronchoscopy to identify the site of bleeding.
Grade ≥2 pulmonary	Discontinue the patient from bevacizumab/placebo. Continue Tarceva.	All Grade 3 hemoptysis adverse events should be reported as serious adverse events (see Section 5.4).
Grade 2 (symptomatic), 3, 4 CNS	Discontinue the patient from bevacizumab/placebo. Continue Tarceva.	All Grade 2 (symptomatic), 3, and 4 CNS hemorrhages should be reported as serious adverse events (see Section 5.4).
Grade 1, 2 non-CNS, non-pulmonary	None.	In patients with bleeding, consider a full hemostasis evaluation, which may include additional INR, bleeding time measurements, and platelet aggregation, etc. In patients with gastrointestinal bleeding, consider stool guaiacs and early use of endoscopy or other studies to identify the location of bleeding.

Table 2 Dosage Modification Criteria and Guidelines for Management of Study Treatment–Related Toxicities (cont.)

NCI CTCAE Grade	Study Drug Dose Modification	Guideline for Management
Hemorrhage (cont'd) [a]		
Grade 3 non-CNS, non-pulmonary	Patients who are also receiving full-dose anticoagulation will be discontinued from bevacizumab/placebo. Continue Tarceva. All other patients will have bevacizumab/placebo held 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. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab/placebo.	As listed above.
Grade 4 non-CNS, non-pulmonary	Discontinue the patient from bevacizumab/placebo. Continue Tarceva.	As listed above.
Hypertension [b]		
Grade 3	Hold bevacizumab/placebo until blood pressure is controlled to systolic ≤150 mmHg and diastolic ≤100 mmHg with standard medication. Continue Tarceva.	Manage with standard oral medications. Common agents given to manage hypertension included calcium channel blockers, diuretics, and ACE inhibitors.
Grade 4, or RPLS confirmed by MRI	Discontinue the patient from bevacizumab/placebo. Continue Tarceva.	As listed above.

Table 2 Dosage Modification Criteria and Guidelines for Management of Study Treatment–Related Toxicities (cont.)

NCI CTCAE Grade	Study Drug Dose Modification	Guideline for Management
Infusion-related adverse events		
Any grade	—	See Section 4.3.3 for the management of infusion-related events for anaphylaxis precautions.
Pulmonary events		
All grades	Temporarily interrupt Tarceva pending diagnostic evaluation. If the pulmonary adverse event is assessed as related to Tarceva, discontinue Tarceva and the treatment phase of the study.	Unexplained pulmonary symptoms, either new or progressive, should be aggressively evaluated.
Rash		
Tolerable rash	None.	Any of the following: minocycline [c], topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course) at the investigator's discretion.
Intolerable rash	Temporarily interrupt Tarceva. Consider temporary or permanent dose reduction of Tarceva if rash persists or worsens over 10–14 days. Continue bevacizumab/placebo.	Manage as described above.
Grade 4	Discontinue the patient from Tarceva and the treatment phase of the study.	As listed above.

Table 2 Dosage Modification Criteria and Guidelines for Management of Study Treatment–Related Toxicities (cont.)

NCI CTCAE Grade	Study Drug Dose Modification	Guideline for Management
Venous thrombosis		
Grade 3 or 4	None.	Patients who require full-dose anticoagulation may be treated with low-molecular-weight heparin or fondaparinux. Patients requiring full-dose anticoagulation with warfarin will be discontinued from bevacizumab/placebo. [d]
Arterial thrombosis (angina, myocardial infarction, transient ischemic attack, cerebrovascular accident and any other arterial thromboembolic event)		
Any grade	Discontinue the patient from bevacizumab/placebo. Continue Tarceva.	Manage per standard of care.
GI perforation		
Requiring medical or surgical therapy	Discontinue the patient from the treatment phase of the study.	Manage per standard of care.
Bowel obstruction		
Grade 1	Continue the patient on study for partial obstruction NOT requiring medical intervention.	Manage per standard of care.
Grade 2	Hold bevacizumab/placebo for partial obstruction requiring medical intervention. The patient may restart upon complete resolution. Continue Tarceva.	Manage per standard of care.

Table 2 Dosage Modification Criteria and Guidelines for Management of Study Treatment–Related Toxicities (cont.)

NCI CTCAE Grade	Study Drug Dose Modification	Guideline for Management
Bowel obstruction (cont.)		
Grade 3, 4	Hold bevacizumab/placebo for complete obstruction. If surgery is necessary, the patient may restart bevacizumab/placebo at least 28 days following surgery, at the investigator's discretion. Continue Tarceva.	Manage per standard of care.
Wound dehiscence		
Requiring medical or surgical therapy	Discontinue the patient from the treatment phase of the study.	Manage per standard of care.
Other (All other events considered related to bevacizumab)		
Grade 3	Hold bevacizumab until recovery to Grade ≤ 1. Continue Tarceva.	—
Grade 4	Discontinue bevacizumab. Continue Tarceva.	—

RPLS = reversible posterior leukoencephalopathy syndrome.

[a] For bleeding occurring in patients on anticoagulation with low-molecular-weight heparin or fondaparinux, assessment of anti-Factor Xa activity and creatinine clearance is recommended.

[b] Hypertension will be monitored through routine blood pressure evaluations; any instance of hypertension will be recorded as an adverse event. Patients who develop Grade 3 hypertension not controlled with medication or Grade 4 hypertension will be discontinued from the treatment phase of the study.

[c] Recommended dose: 200 mg orally twice daily (loading dose) followed by 100 mg orally twice daily for 7–10 days.

[d] Patients on Tarceva who require full-dose anticoagulation may not be anticoagulated with full-dose warfarin; however, patients with indwelling catheters may receive low-dose warfarin for prophylaxis against catheter thrombosis. In this situation, the patient's INR should be closely followed because of a potential drug–drug interaction between Tarceva and warfarin.

Other serious adverse events or Grade 3 or 4 adverse events deemed by the investigator to be related to bevacizumab/placebo or Tarceva should be managed as follows:

If bevacizumab/placebo is the causal drug and the event experienced by the patient is a Grade 4 adverse event, the patient should be permanently discontinued from bevacizumab/placebo. For Grade 3 adverse events, the patient may restart bevacizumab/placebo at the same dose level if the event has resolved to Grade ≤ 1. If, following re-initiation of bevacizumab/placebo, the adverse event recurs at Grade ≥ 2, bevacizumab/placebo should be permanently discontinued. Patients who discontinue bevacizumab have the option of continuing on Tarceva until progressive disease or unmanageable toxicity.

If Tarceva is the causal drug, patients may restart Tarceva at the same dose level or at a reduced dose if the event has resolved to Grade ≤ 1. If, following re-initiation of Tarceva, the adverse event recurs at Grade ≥ 2, Tarceva should again be held until the event has resolved (Grade ≤ 1). Tarceva may be restarted at a reduced dose if the event has resolved to Grade ≤ 1 after the second interruption. If the adverse event recurs after the patient has had two dose reductions, the patient should be permanently discontinued from Tarceva and the treatment phase of the study and should enter survival follow-up.

Dose re-escalation of Tarceva to the next highest level (but never exceeding 150 mg/day) may be attempted at the discretion of the Principal Investigator if toxicity has resolved to Grade ≤ 1 at the reduced dose for ≥ 4 weeks.
If Tarceva is permanently discontinued, the patient must be discontinued from the treatment phase of the study, including permanent discontinuation of bevacizumab/placebo. If a patient is discontinued because of Tarceva toxicity, an unblinding request may be made by the investigator to determine the treatment assignment. No unblinding requests will be necessary as of Amendment 5, as all patients receiving study treatment will have been unblinded and all placebo treatment discontinued.

Subsequent therapy will be provided at the discretion of the treatment clinician.

If either drug is held for ≥ 6 weeks, permanent discontinuation from that drug may be considered.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

Upon enactment of Amendment 6, no information on concomitant therapies will be collected. Prior to Amendment 6, information on concomitant therapies were collected as below.

The following concomitant and excluded therapies are guidelines that should be considered and may be followed by all physicians and patients who elect to remain on study treatment after the enactment of Amendment 5. All treatment decisions are to be made by the treating physician based upon his or her clinical judgment and in accordance with institutional practice and guidelines.

4.4.1 Concomitant Therapies and Procedures

All concomitant medications administered within 14 days preceding the initial study treatment administration on this study through the 30-day Post–Study Treatment Discontinuation Visit were recorded. The reason(s) for treatment, dosage, and dates of treatment should have been reported to the investigator and recorded as instructed on the study-specific Case Report Forms (CRFs).

- Patients should receive full supportive care, including hematopoietic growth factors such as Epogen® (epoetin), transfusions of blood and blood products, antibiotics, etc., when appropriate.
- Use of anti-tumor therapies is permitted after study treatment discontinuation.
- Use of oral contraceptives or hormone-replacement therapy should be continued.
- 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, including ≤ 48 hours of treatment with corticosteroids.
- Patients with indwelling venous catheters may receive prophylaxis against catheter thrombosis in accordance with the local standard of care. Because of a potential drug–drug interaction between Tarceva and warfarin, it is suggested that patient coagulation parameters be monitored if the patient receives low-dose warfarin.
- Full-dose anticoagulation using low-molecular-weight heparin or fondaparinux is permitted, starting either prior to study enrollment or during study participation.
- Concurrent use of anticoagulation and non-steroidal agents are not recommended.
- If patient is undergoing elective surgery, whenever possible at least 56 days should elapse after the last bevacizumab/placebo dose before surgery is performed. Re-initiation of study drug following surgery requires documented approval from the Medical Monitor.
- Prolonged use of systemic corticosteroids for the treatment of skin toxicities is discouraged. Patients who are taking corticosteroids for reasons other than skin toxicity at study entry may continue their use.
- Patients receiving prophylactic or low-dose warfarin or its equivalent require close INR monitoring due to a potential drug–drug interaction with Tarceva
- Other medication considered necessary for the patient's safety and well being may be given at the discretion of the investigator(s).

Because Tarceva is metabolized via the CYP3A4 pathway, agents known to inhibit or induce CYP3A4 function may alter the pharmacokinetics of Tarceva. Although caution and careful monitoring are recommended when use of these compounds is necessary; usage does not exclude patient participation in this study.

4.4.2 Excluded Therapies

The following therapies were excluded during the treatment phase of the study:

- Investigational agents
- Anti-neoplastic or anti-tumor agents, including chemotherapy, radiation therapy, immunotherapy, and hormonal anti-cancer therapy
- Full-dose anticoagulation with warfarin
- Chronic daily use of aspirin (>325 mg/day) or other full-dose NSAIDs with anti-platelet activity
- Dexamethasone for treatment associated with brain metastases

4.5 STUDY ASSESSMENTS

Upon enactment of Amendment 6, data collection will be restricted to spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms, not in the CRF, and handled according to instructions in Section 5.4. Prior to Amendment 6, assessments were conducted as below.

4.5.1 Screening and Pretreatment Assessments

Enrollment in the BETA trial has been completed. Patients should no longer be screened for study participation.

Informed consent was obtained before study-specific screening evaluations were performed and should have been documented in the patient's medical chart.

After written informed consent was obtained and eligibility was confirmed, the study site obtained the patient's identification number and treatment assignment from the IVRS. Patients received their first dose of study treatment on Day 0. All laboratory evaluations were performed by local laboratories.

a. Within 30 Days prior to Randomization

- Signed informed consent(s) were obtained: consent to participate in the study, consent to participate in optional research blood and tissue sampling for additional research, and at selected pharmacokinetic sites, intensive pharmacokinetic blood sampling
- Assessments of disease stage according to Tumor/Node/Metastases (TNM) staging system for lung cancer
- 12-lead electrocardiogram was performed

- Chest X-ray was obtained
- Brain MRI or CT scan was performed
- A radiographic assessment (bidimensional measurement) of all disease sites via MRI or CT scan and evaluate using RECIST was performed
- Patients with squamous cell carcinoma, had CT or MRI scans submitted to Genentech or its designee for confirmation of eligibility prior to randomization
- Concomitant medications for the 14 days prior to randomization were recorded
- Archival paraffin tissue blocks or unstained slides from resected tumor, core biopsy, or fine needle aspirate representative of the patient's primary cancer were located

  This tissue sample, along with a copy of the surgical pathology report from the institution where the original diagnosis was made, was shipped to Genentech or its designee following randomization (see Week 0, Day 0 assessment).

b. Within 7 Days prior to Randomization

- Medical history, including demographics and smoking history using the Smoking History Worksheet was recorded
- Scans from patients with squamous cell carcinoma were submitted to Genentech or its designee at least 5 business days prior to randomization
- Complete physical examination, including height and weight, were performed
- Blood pressure, pulse, and temperature were recorded
- Patients with evidence of hypertension during study screening were evaluated for uncontrolled hypertension in accordance with the JNC 7 guidelines.
- ECOG performance status was recorded
- The following laboratory assessments were performed and evaluated:

  Serum pregnancy test for all females of childbearing potential

  The reason a patient was deemed to be not of childbearing potential in medical history was documented for every female patient not provided with a serum pregnancy test.

  Hematology tests (CBC with differential, platelet count, and INR)

  Serum chemistry and electrolytes (BUN, creatinine, uric acid, sodium, potassium, bicarbonate, chloride, calcium, glucose, LDH, total protein, total bilirubin, AST, ALT, alkaline phosphatase, and albumin)

  Urinalysis and urinary protein to creatinine ratio (spot urine)

  Patients had to have a urinary protein to creatinine ratio < 1 to participate in the study.

  Screening for proteinuria at ex-U.S. sites was performed with a urine dipstick (patients found to have $\geq$ 3+ proteinuria by dipstick had to undergo 24-hour urine collection)

4.5.2 Assessments During Treatment

Patients were treated and assessed according to the plan listed below, before Amendment 5. Changes in the plan may be made after Amendment 5 approval based upon the investigator's clinical judgment and in accordance with institutional standards.

Patients were scheduled to be evaluated at each treatment cycle (every 3 weeks). A window of ± 4 days applied to all visits and all on-study radiographic assessments unless otherwise specified (this does not apply to screening assessments). The interval between bevacizumab infusions could not be < 17 days.

a. Week 0, Day 0

Prior to Study Drug Administration

- Randomized (may occur up to 5 days prior to Day 0, or on Day 0)
- Medical history reviewed
- Archival paraffin tissue block or unstained slides from resected tumor, core biopsy, or fine needle aspirate representative of the patient's primary cancer, shipped once patient was randomized

  This tissue sample, along with a copy of the surgical pathology report from the institution where the original diagnosis was made, was shipped to Genentech within 30 days following randomization.
- Targeted physical examination performed
- Blood pressure, pulse, and temperature recorded
- The following laboratory assessments were performed on Day 0 only if > 1 week has elapsed between screening laboratory tests and Day 0

  Hematology (CBC with differential and platelet count)

  Serum chemistry and electrolytes (BUN, creatinine, uric acid, sodium, potassium, bicarbonate, chloride, calcium, glucose, LDH, total protein, total bilirubin, AST, ALT, alkaline phosphatase, and albumin)

  Urinalysis and urinary protein to creatinine ratio (spot urine)

  Screening for proteinuria at ex-U.S. sites should be performed with a urine dipstick (patients found to have ≥ 3+ proteinuria by dipstick must undergo 24-hour urine collection)

  See Table 2 for dosing guidelines if results are abnormal.
- Collected optional serum and plasma samples for patients who have agreed to participate in additional blood research
- Recorded concomitant medications

During or following Study Drug Administration

- Administered bevacizumab/placebo by infusion

- Dispensed Tarceva bottle(s)/blister pack(s) and instructed patient regarding the administration of Tarceva orally daily for 21 days each cycle

  Patients told to take the first dose of Tarceva in the clinic on Day 0 with ~200 mL (6–8 ounces) of water on an empty stomach at least 1 hour before or 2 hours after a meal. All subsequent doses should be taken at the same time each day with up to ~200 mL (6–8 ounces) of water at least 1 hour before or 2 hours after a meal.

- Recorded adverse events starting on Day 0

b. Week 3 (Day 21) Visit and Every 3 Weeks Thereafter

Prior to Study Drug Administration

- Repeated radiologic studies (CT scan, MRI; chest X-ray when indicated e.g., abnormality previously noted on chest X-ray only) to evaluate disease progression or response every 6 weeks after Day 0, beginning at Week 6 (through Week 24, and then every 12 weeks thereafter), and/or at the Study Treatment Discontinuation Visit using the same method as that used during the baseline assessment.

  Patients with a history of brain metastases underwent head CT scan or MRI every 6 weeks after Day 0 (beginning at Week 6) through Week 24 and then every 12 weeks thereafter and/or at the Study Treatment Discontinuation Visit using the same method as that used during the baseline assessment.

  Performed <u>bidimensional</u> measurements

  Evaluated and documented using RECIST before the next bevacizumab/placebo infusion

  Radiologic assessments could be delayed further for documented adverse events requiring treatment delay; however, the maximum interval between evaluations should not exceed 9 weeks. Any radiologic assessment completed out of this window required a written protocol exception from the Medical Monitor.

- Performed targeted physical examination
- Recorded blood pressure, pulse, and temperature
- Recorded ECOG performance status
- Performed the following laboratory assessments

  Hematology (CBC with differential and platelet count)

  Serum chemistry and electrolytes (BUN, creatinine, uric acid, sodium, potassium, bicarbonate, chloride, calcium, glucose, LDH, total protein, total bilirubin, AST, ALT, alkaline phosphatase, and albumin):
  <u>every 6 weeks</u> after Day 0, beginning at Week 6

  Urinalysis and urinary protein/creatinine ratio (spot urine: <u>every 6 weeks</u> after Day 0, beginning at Week 6

Screening for proteinuria at ex-U.S. sites should be performed with a urine dipstick (patients found to have ≥ 3+ proteinuria by dipstick must undergo 24-hour urine collection)

See Table 2 for dosing guidelines if results were abnormal.

- For intensive pharmacokinetic analysis patients: On Days 21, 22, 42, 63, and 84, bevacizumab/placebo and erlotinib serial serum concentration determinations were collected. Pharmacokinetic analyses for the BETA trial have been completed.
- Recorded concomitant medications
- Recorded adverse events

During or following Study Drug Administration

Sites were made aware of patient treatment assignments in December 2008. Placebo treatment was discontinued for patients randomized to the Tarceva-placebo arm, who remained on study treatment.

The rules below, with the exception of placebo treatment, should be followed until Amendment 5 is approved at your site.

- Administer bevacizumab by infusion

  If the bevacizumab infusion falls outside of the 4-day window, the patient's schedule should be adjusted so that the subsequent bevacizumab/placebo infusion is given 3 weeks after the re-scheduled infusion.
- Collect previously dispensed Tarceva bottle(s)/blister pack(s) and verify patient compliance using a standard tablet count (number of tablets taken divided by the number of days since the last visit)

  Reconcile discrepancies with the patient and document compliance and dates and reasons for all missed doses in the patient's medical chart. Compliance ≤ 80% when unexplained by symptoms or adverse events suggests a need for patient re-education.
- Dispense Tarceva bottle(s)/blister pack(s) and instruct the patient regarding the administration of Tarceva orally daily for 21 days each cycle
- Record adverse events

4.5.3 Study Treatment Discontinuation Visit

Following termination of the study no further information will be collected upon enactment of Amendment 6. Patients will be followed according to the physician's usual standard of care. Prior to Amendment 6, the study termination visit and follow-up assessments were conducted as below.

Patients may remain in the treatment phase of the study until disease progression or until unmanageable toxicity. The treatment phase is completed when both drugs are discontinued. Patients who discontinue bevacizumab have the option of continuing on

Tarceva until progressive disease or unmanageable toxicity. Patients who discontinue Tarceva will be discontinued from the treatment phase of the study, including discontinuation from bevacizumab.

A Study Treatment Discontinuation Visit should be scheduled at the completion of the treatment phase or at the time of the decision to discontinue treatment. The following evaluations and procedures will be performed at the Study Treatment Discontinuation Visit:

- Perform laboratory assessments in keeping with the institutional standard according to the investigator's judgment.
- Collect previously dispensed Tarceva bottle(s)/blister pack(s) and verify patient compliance using a standard tablet count (number of tablets taken divided by the number of days since the last visit)
- Perform radiologic evaluations if warranted by the clinical situation or in accordance with institutional guidelines. Patients with a history of brain metastases must have a CT or MRI of the brain ± 7 days of the treatment discontinuation visit.
- Perform targeted physical examination as per institutional guidelines
- Record adverse events

  Patients who experience an adverse event at treatment completion or at study treatment discontinuation should be followed by the investigator or his or her designee to determine the status of the event until the event is resolved, determined to be irreversible by the investigator, or until the patient begins an alternate form of treatment for their disease (excluding localized radiotherapy).
- Reconcile discrepancies in drug accountability
- Record reason for study treatment discontinuation

4.5.4 30-Day Post–Study Treatment Discontinuation Visit

Patients who are discontinued from the treatment phase should return for a visit ~30 days (28 to 42 days) after the last dose of study treatment for a study assessment. Record adverse events for 30 days following the last dose of either drug.

4.5.5 Follow-Up Assessments

Prior to the final analysis, survival follow-up information was collected via telephone calls and/or clinic visits every 6 weeks (± 2 weeks) until death, loss to follow-up, or study termination by Genentech. Survival follow-up after 30 days after the last dose of study treatment is not required for patients as of Amendment 5, as subsequent information will not alter the primary results of the trial.

4.6 STUDY DRUG DISCONTINUATION

Reasons for study drug (or treatment phase) discontinuation may include, but are not limited to, the following:

- Patient's request to withdraw from study treatment
- Unwillingness or inability to comply with study requirements
- Clinical need for concomitant or ancillary therapy that is not permitted in the study
- Unrelated intercurrent illness that, in the judgment of the Principal Investigator, will affect assessments of clinical status to a significant degree
- Progression of disease
- Unacceptable toxicity
- Completion of the final analysis for the primary endpoint of the trial

It is the right and duty of the investigator to interrupt the treatment of any patient whose health or well-being may be threatened by continuation in this study. Such patients should be withdrawn from the treatment phase of the study, not continued under a modified regimen.

4.7 STUDY TERMINATION

Genentech has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Data recording is inaccurate or incomplete

4.8 STATISTICAL METHODS

The statistical methods noted below were utilized during the interim and final analyses for OSI3364g when appropriate. *Upon enactment of Amendment 6, no further analysis will be done. Data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.*

OSI3364g was a randomized, placebo-controlled trial designed to evaluate the efficacy and safety of bevacizumab in combination with Tarceva relative to Tarceva monotherapy in second-line patients with advanced NSCLC. Two interim analyses were conducted during the study. The first was for safety and the second for safety and efficacy.

Descriptive summaries of continuous data were used to present the group mean, standard deviation, median, minimum, maximum, and sample size. Descriptive summaries of discrete data were used to present the number of patients and incidence as a frequency and as a percentage.

4.8.1 Analysis of the Conduct of the Study

The number of patients randomized were tabulated by center and by treatment arm. Eligibility exceptions and protocol deviations were summarized by treatment arm. Patient disposition was tabulated by treatment arm, and reasons for premature discontinuation were summarized. Tarceva and bevacizumab exposure was also summarized.

4.8.2 Analysis of Treatment Arm Comparability

Treatment arms were assessed for comparability with respect to demographic and baseline characteristics, including age; sex; race; weight; smoking status; histology; disease stage; disease measurability; baseline ECOG performance status; number of metastatic disease sites; history of treated brain metastases; EGFR expression status by IHC; EGFR gene copy number by FISH; and EGFR and Kras mutation status. The baseline value of any variable was defined as the last available value prior to the first administration of study treatment.

4.8.3 Efficacy Analyses

To control the overall Type I error rate at the 5% level, the fixed sequence testing procedure (Westfall and Krishen 2001) was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints. These endpoints were tested in the following order:

- Overall survival
- PFS
- Objective response
- Duration of objective response

No adjustment to the α level will be made for the other analyses.

a. Efficacy Analysis Population

Analyses of overall survival and PFS included all patients who were randomized. For objective response and clinical benefit, only patients with measurable disease at baseline were included in the analysis. For duration of response, only responders were included in the analysis. All analyses were based on the treatment arm to which patients were randomized.

b. Primary Endpoint

The primary efficacy endpoint was overall survival, defined as the period from the date of randomization (as entered in the IVRS) until the date of patient death from any cause. All deaths were included, regardless of whether they occur during treatment or following treatment discontinuation. For patients who have not died, survival data were censored at the date of last contact.

The two-sided log-rank test, stratified by the randomization stratification factors, was used to perform hypothesis testing for assessing the primary study objective. The randomization stratification factors were ECOG performance status (0/1 vs. 2), smoking history (never vs. current/previous), sex (male vs. female), and study site; however, because of the large number of study sites in this trial, study sites will not be included in any efficacy analyses adjusted for randomization stratification factors. Levels of the stratification factors reported on the CRF were used in the analysis. A sensitivity analysis stratified using levels reported on the IVRS was performed. Both analyses were based on the treatment arm to which the patients have been randomized.

An interim efficacy analysis was conducted when approximately 67% of the required deaths (280 deaths) occurred. Overall survival was tested at the significance level determined using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary so that the overall type I error rate will be maintained at the 0.05 level. The DMC recommended that the study continue as planned. The final efficacy analysis was conducted when 418 deaths occurred.

The unstratified log-rank test was performed as a sensitivity analysis. The Kaplan-Meier methods were used to estimate median overall survival for each treatment arm. Cox proportional hazard models, using two models (with and without stratification by the randomization stratification factors), were employed to estimate the hazard ratio (i.e., the magnitude of treatment effect and 95% CI).

c. Secondary Endpoints

Progression-Free Survival. PFS was defined as the time from randomization to documented disease progression or death from any cause on study treatment, whichever occurred earlier. Disease progression was assessed by the investigator according to RECIST. Death on study treatment was defined as death from any cause within 30 days of the last dose of study treatment.

Data for patients without disease progression or patients who had not died on study treatment was censored at the time of the last tumor assessment (or, if no tumor assessments were performed after the baseline visit, at the time of randomization plus 1 day). Analysis methods were the same as those described for overall survival.

Objective Response. Objective response was defined as a complete or partial response determined on two consecutive occasions $\geq$ 4 weeks apart. Only patients with measurable disease at baseline were included in the analysis of the objective response. Patients without a post-baseline tumor assessment were considered non-responders.

An estimate of the ORR and its 95% CI were calculated for each treatment arm. The 95% CI for the treatment difference was also calculated. The Mantel-Haenszel $\chi 2$ test stratified by randomization stratification factors (ECOG performance status

[0/1 vs. 2], smoking history [never vs. current/previous], and sex) was used to compare the treatment groups. An unadjusted Fisher's exact test result was also provided.

Duration of Objective Response. Among patients with an objective response, duration of objective response was defined as the period from the date of initial partial or complete response until the date of disease progression or death from any cause on study treatment. Methods for handling censoring and analysis were the same as those described for PFS. Only patients with an objective response were included in the analysis of duration of objective response.

Evaluation of Relationship between Exploratory Markers and Efficacy Outcomes. To evaluate the effect of exploratory markers on efficacy outcome, efficacy outcomes were summarized for all patients and by treatment arm within each subgroup determined by exploratory markers. Markers considered include the presence or absence of somatic gene mutations of the EGFR pathway, EGFR protein expression by IHC, EGFR gene copy number by FISH, and other markers relevant for the EGFR pathway. The exploration of markers relevant for the VEGF pathway was considered. Efficacy outcomes considered for this analysis included overall survival, PFS, and ORR. Exploratory marker analyses were performed on batched sample sets; results of these analyses were not made available to patients or investigators.

d. Additional Efficacy Analyses

Effect of Risk Factors. The Cox proportional hazards model (when appropriate) was be used to estimate the effect of risk factors on PFS and duration of survival and to evaluate any modifications of treatment effect. To evaluate the effects of risk factors on objective response and to assess modifications of treatment effect, a logistic regression model (if appropriate) were applied.

Clinical Benefit. Clinical benefit was defined as objective response or stable disease maintained for at least 6 weeks. Only patients with measurable disease at baseline were included in the analysis of clinical benefit. The clinical benefit rate was analyzed as described for the ORR.

4.8.4 Pharmacokinetic and Pharmacodynamic Analyses

a. Assessment of the Effect of Bevacizumab on Erlotinib Disposition

Intensive pharmacokinetic sampling was conducted at selected medical centers to evaluate the pharmacokinetic behavior of Tarceva when administered as a single agent or when administered in combination with bevacizumab, and to evaluate the pharmacokinetic behavior of bevacizumab when administered with Tarceva. A subset of at least 17 patients from each treatment arm were scheduled to undergo intensive pharmacokinetic analysis.

Plasma sampling for erlotinib in both arms was performed at Week 3 (Day 21), when erlotinib was at steady state and following the second dose of bevacizumab/placebo . Actual doses and sample collection times were used for pharmacokinetic analysis. The disposition of erlotinib in the presence of bevacizumab was compared with the pharmacokinetic profile of the erlotinib in the monotherapy arm.

Erlotinib and OSI-420 C_{max}, T_{max}, $C_{min,ss}$, $AUC_{0-tau,}$ $C_{max,ss,}$ and CL/F_{ss} (erlotinib only) was estimated by the non-compartmental approach using a validated software program (WinNonlin, version 3.1; Pharsight Corp., Mountain View, CA). OSI-420 is a primary and active metabolite of erlotinib produced by metabolism by the cytochrome P-450 system. Drug interactions could result in alterations in either or both erlotinib and OSI-420 plasma concentrations.

AUC during the dosing interval for both erlotinib and OSI-420 was calculated using standard non-compartmental methods. A 90% CI for the geometric mean ratio (GMR) of the AUC for the Tarceva + bevacizumab and Tarceva + placebo treatment arms was calculated for both erlotinib and OSI-420. Each 90% CI was calculated for the difference of the log-transformed AUCs using the t-distribution and then back-transformed to the ratio scale.

In addition, because AAG is a significant covariate in erlotinib clearance, AAG levels were drawn on Day 21.

b. Assessment of the Effect of Erlotinib on Bevacizumab Disposition

Because there is no arm in which bevacizumab was administered alone (in the absence of erlotinib), the assessment of drug interaction on bevacizumab pharmacokinetics was different than from above. Bevacizumab concentrations in the bevacizumab + erlotinib arm were compared with historical concentration data used in a population pharmacokinetic analysis in cancer patients receiving bevacizumab in Phase I–III studies (Report 03-0324-1751 [Population Pharmacokinetics of Bevacizumab: Structural Model Identification, Mean Population Pharmacokinetic Parameter Estimation, and Covariate Analysis], submitted as part of the Biologics License Application on 25 September 2003). In the population pharmacokinetic analysis, data from eight clinical trials with bevacizumab administered by intravenous infusion were included. A total of 4629 bevacizumab concentrations from 491 patients who received bevacizumab doses ranging from 1 to 20 mg/kg at a dosing frequency ranging from weekly to every 3 weeks were analyzed using a nonlinear mixed-effects modeling approach (NONMEM). This rich dataset from the population pharmacokinetic analysis served as a reference for the comparison with the new bevacizumab concentration data from this trial. Specifically, the effect of Tarceva on bevacizumab pharmacokinetic disposition was evaluated as follows:

- Compare C_{max} and C_{min} at Days 21, 42, 63, and 84 in patients from this study with historically observed values in patients from the population pharmacokinetic database on the same dose schedule of bevacizumab.

- Compare C_{max} and C_{min} at Days 21, 42, 63, and 84 with the simulated concentrations at those times based on the population pharmacokinetic model.

4.8.5 Safety Analyses

Upon enactment of Amendment 6, data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms (not in the CRF), and handled according to instructions in Section 5.4. Prior to Amendment 5 safety assessments were conducted as below.

Safety was assessed through summaries of adverse events and laboratory test results. Patients who receive any amount of study treatment will be included in the safety assessment. Safety results were summarized by the treatment patients actually received for all patients, for patients with squamous cell carcinoma, for patients with brain metastases treated prior to enrollment, and for patients receiving full-dose anticoagulation with low-molecular-weight heparin or fondaparinux.

Safety data collected after the final analysis *was* reviewed and summarized for inclusion in the Investigator's Brochure by Genentech or Genentech's agent.

a. Adverse Events

As clinical data and AEs will no longer be collected in the clinical database, no AEs will be recorded on the CRF.

Verbatim descriptions of treatment-emergent adverse events were mapped to MedDRA thesaurus terms and graded according to the NCI CTCAE, Version 3.0. All adverse events, including Grade 3, 4, and 5 events and serious adverse events, were summarized by treatment arm and NCI CTCAE grade. For each patient's adverse events, the maximum severity recorded were used in the summaries.

b. Laboratory Data

Clinical laboratory tests will be performed at local laboratories. Laboratory toxicities were defined based on local laboratory normal ranges and NCI CTCAE, Version 3.0. Laboratory abnormalities, such as worst toxicity grade and toxicity grade shift from baseline, were summarized by treatment arm.

c. Vital Signs

Changes in blood pressure over time were summarized by treatment arm.

4.8.6 Missing Data

For overall survival, patients who were lost to follow-up were analyzed as censored observations on the date of last contact.

Details of the analyses of missing data were provided in the Statistical Analysis Plan.

4.8.7 Determination of Sample Size

This was a Phase III study to evaluate the efficacy and safety of bevacizumab in combination with Tarceva relative to Tarceva alone in advanced NSCLC. A 33% improvement in survival was considered a clinically significant outcome. To calculate the number of deaths required in this study, the following assumptions were made:

- Two-sided log-rank test
- 83% power at the 5% significance level
- Hazard ratio of bevacizumab + Tarceva versus control (Tarceva alone) of 0.75 corresponding to a 33% improvement in median overall survival from 8 to 10.67 months
- Median overall survival for the control arm is hypothesized based on data from Study BR.21, taking into account the difference in patient population.
- An interim efficacy analysis will be performed when 67% of the required deaths have occurred. The significance level will be determined using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary.
- Five percent of patients will withdraw consent for survival follow-up or will be lost to follow-up.

With these assumptions, 417 deaths were required for the final analysis.

4.8.8 Interim Analyses

The eligible patient population was expanded to include selected patients with squamous cell carcinoma, patients with brain metastases treated prior to enrollment, and patients receiving full-dose anticoagulation with low-molecular-weight heparin or fondaparinux. A DMC monitored the safety of these and all other patients on this trial. The DMC reviewed safety summaries prepared by an external statistical data coordinating center, including monthly serious adverse event reports and thorough interim safety reports. Members of the DMC were external to Genentech and followed a charter that outlined their role and responsibilities. Study personnel remain blinded to study results until the formal unblinding took place in October 2008.

All patients were monitored clinically at 3-week intervals and radiographically at 6-week intervals through Week 24, at which point scans were followed at 12-week intervals. Patients with a history of brain metastases also underwent head CT scans or MRI scans every 6 weeks after Day 0 (beginning at Week 6) through Week 24 and then every 12 weeks thereafter. Summaries of collected serious adverse events were reviewed by the DMC monthly for all patients, for patients with squamous cell carcinoma, and for patients with brain metastases treated prior to enrollment.

All NCI CTCAE Grade $\geq$ 3 hemoptysis and symptomatic Grade $\geq$ 2 CNS hemorrhage events were to be reported as serious adverse events. Grade $\geq$ 3 hemoptysis events were closely monitored for patients with squamous cell carcinoma; enrollment for this subpopulation was to be discontinued if the incidence was unacceptable (for the

stopping guidance, see the DMC charter). Symptomatic Grade ≥ 2 CNS hemorrhage events was closely monitored for patients with brain metastases treated prior to enrollment; accrual for this subpopulation was to be stopped if the incidence was unacceptable (for the stopping guidance, see the DMC charter). Symptomatic Grade ≥ 3 hemorrhage events was closely monitored for patients fully anticoagulated with low-molecular-weight heparin or fondaparinux; accrual for this subpopulation was to be stopped if the incidence of such events was unacceptable.

Two interim analyses were conducted. The first interim analysis was conducted after 123 patients had been enrolled and followed for at least 2 months. Only safety data were assessed in this analysis. The DMC reviewed the interim safety report on 10 July 2006 and recommended that the study continue as planned.

The second interim analysis was conducted when approximately 67% of the required deaths (280 deaths) occurred. Both safety and overall survival were assessed in this analysis. Formal comparisons between the two treatment arms of the incidence of Grade 3–5 and Grade 5 hemoptysis were made. If the incidence in the Tarceva + bevacizumab arm was unacceptable, the study would have been stopped (for the stopping guidance, see the DMC charter). The significance level for the overall survival comparison was determined using the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary of 0.0124 at 67% event time and 0.0462 at the final analysis. The overall survival result was not positive, so the study was continued until 417 deaths occurred.

All summaries/analyses by treatment arm for the DMC review were performed by an independent Data Coordinating Center (DCC). The study team remained blinded to the treatment assignment until study unblinding.

Upon enactment of Amendment 6, data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

4.9 DATA QUALITY ASSURANCE

Genentech supplied CRFs for this study. The CRO entered data directly into the Genentech database via secured access and was responsible for the data management of this study, including double data entry and quality checking of the data. When discrepancies were encountered, the CRO sent requests for data clarification to the sites.

Genentech performed oversight of the data management of this study. Genentech produced a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data were sent directly to Genentech, using Genentech's standard procedures to handle and process the electronic transfer of the data.

CRFs and correction documentation were indexed and imaged. System backups for data stored at Genentech and records retention for the study data were consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF. The plan below was utilized prior to the final analysis of OSI3364g.

5.1 SPECIFICATION OF SAFETY VARIABLES

Safety assessments consisted of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events; measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Death as a result of disease progression was assessed as an efficacy measure and not an AE or SAE.

5.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with NSCLC that were not present prior to the AE reporting period (see Section 5.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period
- Diagnoses and/or symptoms associated with NSCLC should be reported as AEs if they worsen or change in character. Clinical progression of NSCLC should not be reported as an AE.

5.1.2 Serious Adverse Events

An AE should be classified as an SAE if:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as **nonserious AEs**.

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of a specific AE, e.g., mild (Grade 1), moderate (Grade 2), or severe (Grade 3) myocardial infarction (see Section 5.2.2). "Serious" is a regulatory definition (see previous definition) and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

Only serious AEs will be collected after the enactment of Amendment 5. The period of collection will extend to 30 days after treatment discontinuation.

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

5.2 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF. The plan below was utilized prior to the final analysis of OSI3364g.

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in Section 5.1.1, are recorded on the CRF and reported to the Sponsor in accordance with protocol instructions.

Death as a result of disease progression endpoints are only to be assessed as efficacy measures and not as AEs or SAEs.

5.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported began after informed consent was obtained and study treatment was initiated. It ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

SAEs that were observed or reported prior to initiation of study treatment should be recorded as SAEs on the CRF if they were associated with protocol-mandated interventions (e.g., invasive procedures such as biopsies, medication washout, or no treatment run-in).

5.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation timepoints during the study. All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means should be recorded in the patient's medical record and on the appropriate AE or SAE CRF page.

Each recorded AE or SAE should be described by its duration (i.e., start and end dates), severity (see Table 3), regulatory seriousness criteria if applicable, suspected relationship to the investigational product (see following guidance), and actions taken.

The AE grading (severity) scale found in the NCI CTCAE, Version 3.0, should be used for AE reporting.

Table 3 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (<48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 5.1.2) and Table 2.

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- Yes

  There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge.

- No

  Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug).

Note: The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against

cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

5.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

5.3.1 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinical visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.2 Specific Instructions for Recording Adverse Events on the Case Report Form

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF. Avoid colloquialisms and abbreviations.

AEs should be recorded either on an AE CRF page (if no serious criteria are met) or SAE CRF page, but not both.

Only one medical concept should be recorded in the event field on the AE or SAE CRF page.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

c. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation timepoints. Such events should only be recorded once on the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on an AE or SAE CRF page.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent AEs should be recorded on an AE or SAE CRF page.

d. Clinical Laboratory Abnormalities

Individual laboratory abnormalities will generally not be recorded as AEs on the CRF. Only clinically significant laboratory abnormalities that result in study withdrawal, meet serious criteria, are themselves associated with clinical signs or symptoms, or require medical intervention (e.g., low hemoglobin requiring transfusion) will be recorded as AEs or SAEs on the CRF.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the AE or SAE CRF page.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be conveyed as a clinical diagnosis, the diagnosis should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

Only serious AEs will be collected after the initiation of Amendment 5. The period of collection will extend to 30 days after treatment discontinuation. This will focus the safety evaluation of the bevacizumab and Tarceva combination on events of greatest clinical significance.

Upon enactment of Amendment 6, safety data collection will be restricted to the spontaneous reporting of serious adverse events via MedWatch FDA 3500 forms and will not be captured in the CRF.

e. Deaths

For this protocol, mortality was the primary efficacy endpoint. Deaths that occur/occurred during the protocol-specified AE reporting period (see Section 5.2) that are/were attributed by the investigator solely to progression of NSCLC should be recorded only on the Study Discontinuation CRF page. All other on-study deaths, regardless of attribution, should be recorded on an SAE CRF page and expeditiously reported to the Sponsor. An independent monitoring committee will monitor the frequency of death from all causes. After Amendment 5, this will be performed by Genentech or its agent.

When recording a death on an SAE CRF page, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE CRF page. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" on the SAE CRF page.

During post-study survival follow-up, deaths attributed to progression of NSCLC will be recorded only on the Survival and Study Termination CRF pages.

f. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History CRF page.

A preexisting medical condition should be re-assessed throughout the trial and recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE or SAE CRF page, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

g. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE.

If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass on the SAE CRF page.

Hospitalizations for the following reasons will not be recorded as SAEs on the CRF.

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or

- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

h. Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of investigational product, a Pregnancy Report CRF page should be completed and expeditiously submitted to the Sponsor to facilitate outcome follow-up.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, recorded on an SAE CRF page and expeditiously reported to the Sponsor. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to the investigational product should be recorded and reported as an SAE.

i. Poststudy Adverse Events

The investigator should expeditiously notify the study's Sponsor by telephone of any SAE occurring after a patient has completed or discontinued from study participation if attributed to prior investigational product exposure.

The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study.

During the poststudy survival follow-up, deaths attributed to progression of NSCLC will be recorded only on the Survival CRF page.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

For U.S. sites, any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an *MedWatch FDA 3500 form* within *24* hours as described below.

Medical Monitor:	[redacted], M.D.
Telephone No.:	[redacted]
Alternative Telephone No.:	(888) 835-2555

Investigators will submit written reports of all SAEs, regardless of attribution, to Genentech within *24* hours of learning of the events. For initial SAE reports, investigators should record all case details that can be gathered within *24* hours on a *MedWatch 3500 form*. The completed *MedWatch 3500 form* and SAE Fax Cover Sheet should be faxed immediately upon completion to Genentech's Drug Safety Department at:

(650) 225-4682
or
(650) 225-5288

Relevant follow-up information should be submitted to Genentech's Drug Safety as soon as it becomes available and/or upon request.

Note: All non-U.S. sites were closed prior to the enactment of Amendment 6.

5.5 TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

All SAEs that are encountered during the protocol-specified AE reporting period should be followed to their resolutions, or until the investigator assesses them as stable, or the patient is lost to follow-up. Resolution of SAEs (with dates) should be documented *via a MedWatch FDA 3500 form.*

For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

The safety data collected after the final analysis of OSI3364g will be reviewed on a regular basis by Genentech or its agent. The findings will be recorded in the annual Investigator's Brochure. If a new safety signal is identified, a safety evaluation following Genentech standard operating procedures (SOPs) will be conducted and the data reported in keeping with the SOP guidance.

6. INVESTIGATOR REQUIREMENTS

The requirements listed below were required prior to the final analysis of OSI3364g. These should be continued unless stated otherwise.

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with Genentech or a Genentech representative:

- Original U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae of the Principal Investigator and all subinvestigators
- Complete financial disclosure forms for the Principal Investigator and all subinvestigators listed on the U.S. FDA Form 1572
- Institutional Review Board (IRB) or Ethics Committee (EC) membership list and/or Department of Health and Human Services number
- Written documentation of IRB/EC approval of protocol (identified by Genentech protocol number or title and date of approval) and Informed Consent Form (identified by Genentech protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form
- Written documentation of IRB/EC review and approval of any advertising materials to be used for study recruitment, if applicable

  Genentech or its designee must review any proposed deviations from the sample Informed Consent Form. The Genentech Legal Department must review and approve any advertising materials.
- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- A signed Clinical Research Agreement
- Certified translations of IRB/EC approval letters, pertinent correspondence, and approved Informed Consent Form (when applicable)
- A signed and dated Protocol Acceptance Form
- Other region specific documents, as required

6.2 STUDY COMPLETION

Study OSI3364g is considered complete and no further patient data will be collected, except for serious adverse event reporting via MedWatch FDA 3500 Forms, (not in the CRF), and will be handled according to instructions in Section 5.4.

The following data and materials are required by Genentech before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period (or the study termination visit after Amendment 5)
- CRFs (including correction forms) properly completed by appropriate study personnel and signed and dated by the investigator
- Completed Drug Accountability Records (IND Retrieval Record [INDRR-1], Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (will accept IRB/EC summary close letter)
- All regulatory documents (e.g., curriculum vitae for each Principal Investigator, U.S. FDA Form 1572 for each site)
- A signed and dated protocol amendment acceptance form (if applicable)
- Updated financial disclosure forms for the Principal Investigator and all subinvestigators listed on the U.S. FDA Form 1572 (applicable for 1 year after the last patient has completed the study)
- Other region specific documents, as required

6.3 INFORMED CONSENT

The Informed Consent Form has been revised to reflect the changes made to the protocol under Amendment 6. Following submission and IRB approval of Amendment 6, only those patients who are currently receiving study treatment will be required to be reconsented with the amended Informed Consent Form.

Sample Informed Consent Forms will be provided to each site. Genentech or its designee must review any proposed deviations from the sample Informed Consent Form. The final IRB/EC-approved document must be provided to Genentech for regulatory purposes.

The Informed Consent Form must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the Informed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

For patients unable to read or write, the Informed Consent Form should be read to the patient by a person other than the patient's relative/friend or the study staff (e.g., site staff not working on this study).

Signed Informed Consent Form must remain in each patient's study file and must be available for verification by study monitors at any time.

6.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the Informed Consent Form, and relevant supporting information must be submitted to the IRB/EC for review and must be approved before the study is initiated. In addition, any advertising materials must be approved by the IRB/EC. The study will be conducted in accordance with U.S. FDA, applicable national and local health authority, and IRB/EC requirements.

The Principal Investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB/EC must be updated at least once a year. The Principal Investigator must also keep the IRB/EC informed of any significant AEs.

Investigators are required to promptly notify their respective IRB/EC of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator Brochure and that are considered by the investigator to be possibly or probably related to the study drug. Some IRBs or ECs may have other specific adverse event requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB/EC any written safety report or update provided by Genentech (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by Genentech or an authorized Genentech representative to inspect study data, patients' medical records, and CRFs in accordance with current U.S. GCPs and the respective local and national government regulations and guidelines (if applicable).

The Principal Investigator will permit authorized representatives of Genentech, the U.S. FDA, and the respective national or local health authorities to inspect facilities and records relevant to this study.

Upon enactment of Amendment 6, all necessary study monitoring and site management will be performed remotely.

6.6 CASE REPORT FORMS

CRFs will be supplied by Genentech and should be handled in accordance with instructions from Genentech.

All CRFs should be filled out completely by examining personnel or the study coordinator. The CRF should be reviewed, signed, and dated by the investigator.

All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced CRF copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID ON THE ORIGINAL.

6.7 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification (SDV) to confirm that critical protocol data (i.e., source data) transcribed on the CRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data transcribed on the CRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

6.8 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents ability to delete or alter previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the study monitor, Genentech's Computer Systems Compliance group will assess whether electronic records generated from computerized medical

record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents will need to be maintained to ensure that critical protocol data that are transcribed on the CRFs can be verified.

6.9 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech *and Astellas Pharmaceuticals*. The recipient will acknowledge receipt of the drug by returning the *enclosed paperwork that is received with study medication shipments*. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the Drug Inventory Log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure only after study drug reconciliation has been performed and disposal has been authorized by a Genentech representative.

All forms will be supplied by Genentech.

6.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, Genentech, and the IRB/EC for each study site, if appropriate.

6.11 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the International Council on Harmonisation (ICH) Guideline for Good Clinical Practice (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs,
consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local

laws for retention of records also apply. Genentech will notify the Principal Investigator of these events.

No records should be disposed of without the written approval of Genentech.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with U.S. FDA IND regulations and with those of the relevant national and local health authorities.

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Appendix A
Study Flowchart

Study Period	Screening	Treatment								Survival Follow-Up
Week		0	3	6	9	12				Every 6 Weeks after Study Treatment Discontinuation
Day	–30	0	21	42	63	84	Every 3 Weeks	Every 6 Weeks	Study Treatment Discontinuation Visit [a]	
Written informed consent(s)	x									
Medical history	x	x								
Demographics	x									
Assess disease stage using TNM	x									
12-lead electrocardiogram	x									
Chest X-ray	x									
Brain MRI or CT scan	x								x [b]	
Tumor assessments CT/MRI	x									
Archival tissue sample [c]	x									
Complete physical examination	x									
Height and weight	x									
Blood pressure, pulse, and temperature	x									
ECOG performance status	x									
Serum pregnancy test	x									
CBC, differential, and platelet count	x									
INR	x									
Serum chemistry and electrolytes	x									
Urinalysis, protein to creatinine ratio	x									
Bevacizumab administration		x	x	x	x	x	x			
Dispense/collect Tarceva [d]							x		x	
Concomitant medications	x									
Adverse events [e]							x		x	

Appendix A
Study Flowchart (cont'd)

[a] A Study Treatment Discontinuation Visit should be scheduled at the completion of the treatment phase or at the decision to discontinue treatment. Another visit should be scheduled for ~30 days (28–42 days) after the end of study treatment to assess adverse events.

[b] Brain MRI or CT scan for patients with a history of brain metastases.

[c] An archival paraffin tissue block or unstained slides (preferably 10 or more) from tumor resection, core biopsy, or fine needle aspirate.

[d] Dispense Tarceva and collect Tarceva bottles dispensed at previous visit, if applicable; verify patient compliance. Tarceva tablets should be taken at the same time each day with ~200 mL (6–8 ounces) of water on an empty stomach at least 1 hour before or 2 hours after a meal.

[e] Serious adverse events will be recorded starting on Day 0 and for 30 days following the last dose of study treatment (or the decision to discontinue study treatment).

Appendix B
Tarceva® Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TARCEVA safely and effectively. See full prescribing information for TARCEVA.

TARCEVA® (erlotinib) tablets, oral

Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Elevated International Normalized Ratio and Potential Bleeding (5.11) 04/2012

----------INDICATIONS AND USAGE----------

TARCEVA is a kinase inhibitor indicated for:

- Maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1)
- Treatment of locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. (1.1)
- First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- The dose for NSCLC is 150 mg/day. (2.1)
- The dose for pancreatic cancer is 100 mg/day. (2.2)
- All doses of TARCEVA should be taken on an empty stomach at least one hour before or two hours after food. (2.1, 2.2)
- Reduce in 50 mg decrements, when necessary. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 25 mg, 100 mg and 150 mg. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Interstitial Lung Disease (ILD)-like events, including fatalities have been infrequently reported. Interrupt TARCEVA if acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever occur. Discontinue TARCEVA if ILD is diagnosed. (5.1)
- Cases of acute renal failure (including fatalities), and renal insufficiency have been reported. Interrupt TARCEVA in the event of dehydration. Monitor renal function and electrolytes in patients at risk of dehydration. (5.2)
- Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported. Monitor periodic liver function testing. Interrupt or discontinue TARCEVA if liver function changes are severe. (5.3)
- Monitor patients with hepatic impairment closely. Interrupt or discontinue TARCEVA if changes in liver function are severe (5.4)
- Gastrointestinal perforations, including fatalities, have been reported. Discontinue TARCEVA. (5.5)
- Bullous and exfoliative skin disorders, including fatalities, have been reported. Interrupt or discontinue TARCEVA (5.6)
- Myocardial infarction/ischemia has been reported, including fatalities, in patients with pancreatic cancer. (5.7)
- Cerebrovascular accidents, including a fatality, have been reported in patients with pancreatic cancer. (5.8)
- Microangiopathic Hemolytic Anemia with thrombocytopenia has been reported in patients with pancreatic cancer. (5.9)
- Corneal perforation and ulceration have been reported. Interrupt or discontinue TARCEVA (5.10)
- International Normalized Ratio (INR) elevations and bleeding events (including fatalities), associated with concomitant warfarin administration have been reported. Monitor patients taking warfarin or other coumarin-derivative anticoagulants. (5.11)
- TARCEVA can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid pregnancy while on TARCEVA. (5.12)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (>20%) in maintenance treatment are rash-like events and diarrhea. (6)
- The most common adverse reactions (>20%) in 2nd line NSCLC are rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, infection and vomiting. (6)
- The most common adverse reactions (>20%) in pancreatic cancer are fatigue, rash, nausea, anorexia, diarrhea, abdominal pain, vomiting, weight decrease, infection, edema, pyrexia, constipation, bone pain, dyspnea, stomatitis and myalgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact OSI Pharmaceuticals, LLC, at 1-800-572-1932 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A4 inhibitors may increase erlotinib plasma concentrations. (7)
- CYP3A4 inducers may decrease erlotinib plasma concentrations. (7)
- CYP1A2 inducers may decrease erlotinib plasma concentrations. (7)
- Erlotinib solubility is pH dependent. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its absorption. (7)
- Cigarette smoking decreases erlotinib plasma concentrations (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [04/2012]

FULL PRESCRIBING INFORMATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed.

Appendix B
Tarceva® Package Insert (cont.)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer (NSCLC)

TARCEVA monotherapy is indicated for the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy *[see Clinical Studies (14.1)]*.

TARCEVA monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen *[see Clinical Studies (14.2)]*.

Results from two, multicenter, placebo-controlled, randomized, Phase 3 trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel or gemcitabine and cisplatin] and its use is not recommended in that setting *[see Clinical Studies (14.3)]*.

1.2 Pancreatic Cancer

TARCEVA in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose - NSCLC

The recommended daily dose of TARCEVA for NSCLC is 150 mg taken on an empty stomach at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond progression is beneficial.

2.2 Recommended Dose - Pancreatic Cancer

The recommended daily dose of TARCEVA for pancreatic cancer is 100 mg taken on an empty stomach at least one hour before or two hours after the ingestion of food, in combination with gemcitabine *[see Clinical Studies (14.4) or the gemcitabine package insert]*. Treatment should continue until disease progression or unacceptable toxicity occurs.

2.3 Dose Modifications

In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with TARCEVA should be interrupted pending diagnostic evaluation. If Interstitial Lung Disease (ILD) is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as necessary *[see Warnings and Precautions (5.1)]*. Discontinue TARCEVA for hepatic failure or gastrointestinal perforation. Interrupt or discontinue TARCEVA in patients with dehydration who are at risk for renal failure, in patients with severe bullous, blistering or exfoliative skin conditions, or in patients with acute /worsening ocular disorders *[see Warnings and Precautions (5.2, 5.3, 5.4, 5.5, 5.6, 5.10)]*.

Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require dose reduction or temporary interruption of therapy.

When dose reduction is necessary, the TARCEVA dose should be reduced in 50 mg decrements.

In patients who are taking TARCEVA with a strong CYP3A4 inhibitor such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice, a dose reduction should be considered if severe adverse reactions occur. Similarly, in patients who are taking TARCEVA with an inhibitor of both CYP3A4 and CYP1A2 like ciprofloxacin, a dose reduction of TARCEVA should be considered if severe adverse reactions occur *[see Drug Interactions (7)]*.

Appendix B
Tarceva® Package Insert (cont.)

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3 to 4/5. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, an increase in the dose of TARCEVA should be considered as tolerated at two week intervals while monitoring the patient's safety. The maximum dose of TARCEVA studied in combination with rifampicin is 450 mg. If the TARCEVA dose is adjusted upward, the dose will need to be reduced immediately to the indicated starting dose upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort. These too should be avoided if possible *[see Drug Interactions (7)]*.

Cigarette smoking has been shown to reduce erlotinib exposure. Patients should be advised to stop smoking. If a patient continues to smoke, a cautious increase in the dose of TARCEVA, not exceeding 300 mg may be considered, while monitoring the patient's safety. However, efficacy and long-term safety (> 14 days) of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes. If the TARCEVA dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking *[see Clinical Pharmacology (12.3)]*.

Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B), patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA [*see Warnings and Precautions (5.4)]*. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range. In the setting of worsening liver function tests, before they become severe, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. TARCEVA dosing should be interrupted or discontinued if total bilirubin is >3 x ULN and/or transaminases are >5 x ULN in the setting of normal pretreatment values *[see Warnings and Precautions (5.3, 5.4), Adverse Reactions (6.1, 6.2) and Use in Specific Populations (8.8)]*.

3 DOSAGE FORMS AND STRENGTHS

25 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side.

100 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side.

150 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Toxicity

There have been reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the randomized single-agent NSCLC-studies *[see Clinical Studies (14.1, 14.2)]*, the incidence of serious ILD-like events in the TARCEVA treated patients versus placebo treated patients was 0.7% versus 0% in the maintenance study and 0.8% for both groups in the 2nd and 3rd line study. In the pancreatic cancer study - in combination with gemcitabine – *[see Clinical Studies (14.4)]*, the incidence of ILD-like events was 2.5% in the TARCEVA plus gemcitabine group vs. 0.4% in the placebo plus gemcitabine group.

The overall incidence of ILD-like events in approximately 32,000 TARCEVA-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 1.1%.

Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after initiating TARCEVA therapy. In the lung cancer trials most of the cases were associated with

Appendix B
Tarceva® Package Insert (cont.)

confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of an acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever, TARCEVA therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as needed *[see Dosage and Administration (2.3)]*.

5.2 Renal Failure

Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia or concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (eg, pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), TARCEVA therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration *[see Adverse Reactions (6.1) and Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of TARCEVA, particularly in patients with baseline hepatic impairment. Therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) is recommended. In the setting of worsening liver function tests, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. TARCEVA dosing should be interrupted or discontinued if total bilirubin is >3 x ULN and/or transaminases are >5 x ULN in the setting of normal pretreatment values *[see Adverse Reactions (6.1, 6.2) and Dosage and Administration (2.3)]*.

5.4 Patients with Hepatic Impairment

In a pharmacokinetic study in patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 out of 15 patients died on treatment or within 30 days of the last TARCEVA dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin > 3 x ULN suggesting severe hepatic impairment. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.3)]*.

5.5 Gastrointestinal Perforation

Gastrointestinal perforation (including fatalities) have been reported in patients receiving TARCEVA. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. *[see Adverse Reactions (6.1, 6.2)]*. Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation.

5.6 Bullous and Exfoliative Skin Disorders

Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal *[see Adverse Reactions (6.1, 6.2)]*. Interrupt or discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions.

Appendix B
Tarceva® Package Insert (cont.)

5.7 Myocardial Infarction/Ischemia

In the pancreatic carcinoma trial, six patients (incidence of 2.3%) in the TARCEVA/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, 3 patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.2%) and one died due to myocardial infarction.

5.8 Cerebrovascular Accident

In the pancreatic carcinoma trial, six patients in the TARCEVA/gemcitabine group developed cerebrovascular accidents (incidence: 2.3%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents.

5.9 Microangiopathic Hemolytic Anemia with Thrombocytopenia

In the pancreatic carcinoma trial, two patients in the TARCEVA/gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence: 0.8%). Both patients received TARCEVA and gemcitabine concurrently. In comparison, in the placebo/gemcitabine group there were no cases of microangiopathic hemolytic anemia with thrombocytopenia.

5.10 Ocular Disorders

Corneal perforation or ulceration have been reported during use of TARCEVA. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with TARCEVA treatment and are known risk factors for corneal ulceration/perforation *[see Adverse Reactions (6.1)]*. Interrupt or discontinue TARCEVA therapy if patients present with acute/worsening ocular disorders such as eye pain.

5.11 Elevated International Normalized Ratio and Potential Bleeding

International Normalized Ratio (INR) elevations and bleeding events, including gastrointestinal and non-gastrointestinal bleeding (including fatalities), have been reported, associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR *[see Adverse Reactions (6.1) and Drug Interactions (7)]*.

5.12 Use in Pregnancy

TARCEVA can cause fetal harm when administered to a pregnant woman. Erlotinib administered to rabbits during organogenesis at doses that result in plasma drug concentrations of approximately 3 times those in humans at the recommended dose of 150 mg daily, was associated with embryofetal lethality and abortion. When erlotinib was administered to female rats prior to mating and through the first week of pregnancy, at doses 0.3 or 0.7 times the clinical dose of 150 mg, on a mg/m^2 basis, there was an increase in early resorptions that resulted in a decrease in the number of live fetuses *[see Use in Specific Populations (8.1)]*.

There are no adequate and well-controlled studies in pregnant women using TARCEVA. Women of childbearing potential should be advised to avoid pregnancy while on TARCEVA. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. If TARCEVA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

6 ADVERSE REACTIONS

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

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

There have been reports of serious events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors *[see Warnings and Precautions (5) and Dosage and Administration (2.3)]*.

Appendix B
Tarceva® Package Insert (cont.)

6.1 Clinical Trial Experience

Non-Small Cell Lung Cancer

Maintenance Study

Adverse reactions, regardless of causality, that occurred in at least 3% of patients treated with single-agent TARCEVA at 150 mg and at least 3% more often than in the placebo group in the randomized maintenance trial are summarized by NCI-CTC (version 3.0) Grade in Table 1.

The most common adverse reactions in patients receiving single-agent TARCEVA 150 mg were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 6.0% and 1.8%, respectively, in TARCEVA-treated patients. Rash and diarrhea resulted in study discontinuation in 1.2% and 0.3% of TARCEVA-treated patients, respectively. Dose reduction or interruption for rash and diarrhea was needed in 5.1% and 2.8% of patients, respectively. In TARCEVA-treated patients who developed rash, the onset was within two weeks in 66% and within one month in 81%.

Table 1: NSCLC Maintenance Study: Adverse Reactions Occurring More Frequently (≥ 3%) in the Single-Agent TARCEVA Group than in the Placebo Group and in ≥ 3% of Patients in the TARCEVA Group.

	TARCEVA N = 433			PLACEBO N = 445		
NCI-CTC Grade	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
MedDRA Preferred Term	%	%	%	%	%	%
Rash	49.2	6.0	0	5.8	0	0
Diarrhea	20.3	1.8	0	4.5	0	0
Fatigue	9.0	1.8	0	5.8	1.1	0
Anorexia	9.2	<1	0	4.9	<1	0
Pruritus	7.4	<1	0	2.7	0	0
Acne	6.2	<1	0	0	0	0
Dermatitis Acneiform	4.6	<1	0	1.1	0	0
Dry Skin	4.4	0	0	<1	0	0
Weight Decreased	3.9	<1	0	<1	0	0
Paronychia	3.9	<1	0	0	0	0

Appendix B
Tarceva® Package Insert (cont.)

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent TARCEVA 150 mg in the Maintenance study. Grade 2 (>2.5 – 5.0 x ULN) ALT elevations occurred in 2% and 1%, and Grade 3 (>5.0 – 20.0 x ULN) ALT elevations were observed in 1% and 0% of TARCEVA and placebo treated patients, respectively. The TARCEVA treatment group had Grade 2 (>1.5-3.0 x ULN) bilirubin elevations in 4% and Grade 3 (>3.0-10.0 x ULN) in <1% compared with <1% for both Grades 2 and 3 in the placebo group. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

Second/Third Line Study

Adverse reactions, regardless of causality, that occurred in at least 10% of patients treated with single-agent TARCEVA at 150 mg and at least 3% more often than in the placebo group in the randomized trial of patients with NSCLC are summarized by NCI-CTC (version 2.0) Grade in Table 2.

The most common adverse reactions in this patient population were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in TARCEVA-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of TARCEVA-treated patients. Six percent and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

Table 2: NSCLC 2nd/3rd Line Study: Adverse Reactions Occurring More Frequently (≥ 3%) in the Single-agent TARCEVA 150 mg Group than in the Placebo Group and in ≥10% of Patients in the TARCEVA Group.

	TARCEVA 150 mg N = 485			Placebo N = 242		
NCI-CTC Grade	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
MedDRA Preferred Term	%	%	%	%	%	%
Rash	75	8	<1	17	0	0
Diarrhea	54	6	<1	18	<1	0
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

Appendix B
Tarceva® Package Insert (cont.)

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent TARCEVA 150 mg. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5 – 5.0 x ULN) ALT elevations occurred in 4% and <1% of TARCEVA and placebo treated patients, respectively. Grade 3 (>5.0 – 20.0 x ULN) elevations were not observed in TARCEVA-treated patients. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

Pancreatic Cancer

Adverse reactions, regardless of causality, that occurred in at least 10% of patients treated with TARCEVA 100 mg plus gemcitabine in the randomized trial of patients with pancreatic cancer are summarized by NCI-CTC (version 2.0) Grade in Table 3.

The most common adverse reactions in pancreatic cancer patients receiving TARCEVA 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea. In the TARCEVA plus gemcitabine arm, Grade 3/4 rash and diarrhea were each reported in 5% of TARCEVA plus gemcitabine-treated patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving TARCEVA plus gemcitabine. The 150 mg cohort was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption.

Table 3: Adverse Reactions Occurring in ≥ 10% of TARCEVA-treated Pancreatic Cancer Patients: 100 mg cohort

	TARCEVA + Gemcitabine 1000 mg/m^2 IV N=259			Placebo + Gemcitabine 1000 mg/m^2 IV N=256		
NCI-CTC Grade	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
MedDRA Preferred Term	%	%	%	%	%	%
Fatigue	73	14	2	70	13	2
Rash	69	5	0	30	1	0
Nausea	60	7	0	58	7	0
Anorexia	52	6	<1	52	5	<1
Diarrhea	48	5	<1	36	2	0
Abdominal pain	46	9	<1	45	12	<1
Vomiting	42	7	<1	41	4	<1
Weight decreased	39	2	0	29	<1	0
Infection*	39	13	3	30	9	2
Edema	37	3	<1	36	2	<1
Pyrexia	36	3	0	30	4	0
Constipation	31	3	1	34	5	1
Bone pain	25	4	<1	23	2	0
Dyspnea	24	5	<1	23	5	0
Stomatitis	22	<1	0	12	0	0
Myalgia	21	1	0	20	<1	0

Appendix B
Tarceva® Package Insert (cont.)

	TARCEVA + Gemcitabine 1000 mg/m² IV N=259			Placebo + Gemcitabine 1000 mg/m² IV N=256		
NCI-CTC Grade	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Depression	19	2	0	14	<1	0
Dyspepsia	17	<1	0	13	<1	0
Cough	16	0	0	11	0	0
Dizziness	15	<1	0	13	0	<1
Headache	15	<1	0	10	0	0
Insomnia	15	<1	0	16	<1	0
Alopecia	14	0	0	11	0	0
Anxiety	13	1	0	11	<1	0
Neuropathy	13	1	<1	10	<1	0
Flatulence	13	0	0	9	<1	0
Rigors	12	0	0	9	0	0

*Includes all MedDRA preferred terms in the Infections and Infestations System Organ Class

In the pancreatic carcinoma trial, 10 patients in the TARCEVA/gemcitabine group developed deep venous thrombosis (incidence: 3.9%). In comparison, 3 patients in the placebo/gemcitabine group developed deep venous thrombosis (incidence 1.2%). The overall incidence of grade 3 or 4 thrombotic events, including deep venous thrombosis, was similar in the two treatment arms: 11% for TARCEVA plus gemcitabine and 9% for placebo plus gemcitabine.

No differences in Grade 3 or Grade 4 hematologic laboratory toxicities were detected between the TARCEVA plus gemcitabine group compared to the placebo plus gemcitabine group.

Severe adverse reactions (≥grade 3 NCI-CTC) in the TARCEVA plus gemcitabine group with incidences < 5% included syncope, arrhythmias, ileus, pancreatitis, hemolytic anemia including microangiopathic hemolytic anemia with thrombocytopenia, myocardial infarction/ischemia, cerebrovascular accidents including cerebral hemorrhage, and renal insufficiency *[see Warnings and Precautions (5)]*.

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been observed following the administration of TARCEVA plus gemcitabine in patients with pancreatic cancer. Table 4 displays the most severe NCI-CTC grade of liver function abnormalities that developed. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

Table 4 **Liver Function Test Abnormalities (most severe NCI-CTC grade) in Pancreatic Cancer Patients: 100 mg Cohort**

	TARCEVA + Gemcitabine 1000 mg/m² IV N = 259			Placebo + Gemcitabine 1000 mg/m² IV N = 256		
NCI-CTC Grade	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Bilirubin	17 %	10%	<1%	11%	10%	3%
ALT	31%	13%	<1%	22%	9%	0%

Appendix B
Tarceva® Package Insert (cont.)

	TARCEVA + Gemcitabine 1000 mg/m² IV N = 259			Placebo + Gemcitabine 1000 mg/m² IV N = 256		
NCI-CTC Grade	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
AST	24%	10%	<1%	19%	9%	0%

NSCLC and Pancreatic Indications: Low Frequency Adverse Reactions

Gastrointestinal Disorders

Gastrointestinal perforations have been reported *[see Warnings and Precautions (5.5)]*.

Cases of gastrointestinal bleeding (including fatalities) have been reported, some associated with concomitant warfarin or NSAID administration *[see Warnings and Precautions (5.11) and Drug Interactions (7)]*. These adverse reactions were reported as peptic ulcer bleeding (gastritis, gastroduodenal ulcers), hematemesis, hematochezia, melena and hemorrhage from possible colitis.

Renal Disorders

Cases of acute renal failure or renal insufficiency, including fatalities, with or without hypokalemia have been reported *[see Warnings and Precautions (5.2)]*.

Hepatic Disorders

Hepatic failure has been reported in patients treated with single-agent TARCEVA or TARCEVA combined with chemotherapy *[see Warnings and Precautions (5.3)]*.

Ocular Disorders

Corneal ulcerations or perforations have been reported in patients receiving TARCEVA treatment. Abnormal eyelash growth including in-growing eyelashes, excessive growth and thickening of the eyelashes have been reported *[see Warnings and Precautions (5.10)]* and are risk factors for corneal ulceration/perforation.

NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving TARCEVA therapy in the NSCLC and pancreatic cancer clinical trials. *[see Patient Counseling Information (17)]*.

Skin, Hair and Nail Disorders

Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis *[see Warnings and Precautions (5.6)]*.

In patients who develop skin rash, the appearance of the rash is typically erythematous and maculopapular and it may resemble acne with follicular pustules, but is histopathologically different. This skin reaction commonly occurs on the face, upper chest and back, but may be more generalized or severe (NCI-CTC Grade 3 or 4) with desquamation. Skin reactions may occur or worsen in sun exposed areas; therefore, the use of sunscreen or avoidance of sun exposure is recommended. Associated symptoms may include itching, tenderness and/or burning. Also, hyperpigmentation or dry skin, with or without digital skin fissures have been reported and in the majority of cases were associated with rash.

Hair and nail disorders including alopecia, hirsutism, eyelash/eyebrow (see above) changes, paronychia and brittle and loose nails have been reported.

Appendix B
Tarceva® Package Insert (cont.)

Other Disorders

Epistaxis was also reported in both the single-agent NSCLC and the pancreatic cancer clinical trials.

In general, no notable differences in the safety of TARCEVA monotherapy or in combination with gemcitabine could be discerned between females or males and between patients younger or older than the age of 65 years *[see Use in Specific Populations (8.5 and 8.6)]*. The safety of TARCEVA appears similar in Caucasian and Asian patients.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of TARCEVA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders

Hair and nail changes, mostly non-serious e.g. hirsutism, eyelash/eyebrow changes, paronychia and brittle and loose nails. Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis *[see Warnings and Precautions (5.6)]*.

Gastrointestinal Disorders

Gastrointestinal perforations *[see Warnings and Precautions (5.5)]*.

Hepatic Disorders

Hepatic failure has been reported in patients treated with single-agent TARCEVA or TARCEVA combined with chemotherapy *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 2/3. When TARCEVA was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure [AUC] and maximum concentration [C_{max}] increased by 39% and 17% respectively. Caution should be used when administering or taking TARCEVA with ketoconazole and other strong CYP3A4 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole and grapefruit or grapefruit juice *[see Dosage and Administration (2.3)]*.

Pre-treatment with the CYP3A4 inducer rifampicin for 7 days prior to TARCEVA decreased erlotinib AUC by about 2/3 to 4/5, which is equivalent to a dose of about 30 to 50 mg in NSCLC patients. In a separate study, treatment with rifampicin for 11 days, with co-administration of a single 450 mg dose of TARCEVA on day 8 resulted in a mean erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg TARCEVA dose in the absence of rifampicin treatment *[see Dosage and Administration (2.3)]*. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, adjusting the starting dose should be considered. If the TARCEVA dose is adjusted upward, the dose will need to be reduced immediately to the indicated starting dose upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort *[see Dosage and Administration (2.3)]*.

Cigarette smoking has been shown to reduce erlotinib AUC. Patients should be advised to stop smoking; however, if they continue to smoke, a cautious increase in the dose of TARCEVA may be considered, while monitoring the patient's safety. If the TARCEVA dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Pretreatment and co-administration of TARCEVA decreased the AUC of CYP3A4 substrate, midazolam, by 24%. The mechanism is not clear.

Appendix B
Tarceva® Package Insert (cont.)

In a study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and reduce its bioavailability. Increasing the dose of TARCEVA when co-administered with such agents is not likely to compensate for the loss of exposure. Co-administration of TARCEVA with omeprazole, a proton pump inhibitor, decreased the erlotinib AUC by 46%. Since proton pump inhibitors affect pH of the upper GI tract for an extended period, separation of doses may not eliminate the interaction. The concomitant use of proton pump inhibitors with TARCEVA should be avoided if possible. Co-administration of TARCEVA with 300 mg ranitidine, an H_2 receptor antagonist, decreased erlotinib AUC by 33%. When TARCEVA was administered with ranitidine 150 mg twice daily (at least 10 h after the previous ranitidine evening dose and 2 h before the ranitidine morning dose), the erlotinib AUC decreased by 15%. If patients need to be treated with an H_2-receptor antagonist such as ranitidine, it should be used in a staggered manner. TARCEVA must be taken once a day, 10 hours after the H_2-receptor antagonist dosing and at least 2 hours before the next dose of H_2-receptor antagonist. Although the effect of antacids on erlotinib pharmacokinetics has not been evaluated, the antacid dose and the TARCEVA dose should be separated by several hours, if an antacid is necessary. *[see Clinical Pharmacology (12.3)]*.

Interaction with coumarin-derived anticoagulants, including warfarin, leading to increased International Normalized Ratio (INR) and bleeding events, which in some cases were fatal, have been reported in patients receiving TARCEVA. Patients taking coumarin derived anticoagulants should be monitored regularly for any changes in prothrombin time or INR *[see Warnings and Precautions (5.11) and Adverse Reactions (6.1)]*

The combination of TARCEVA and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely. The mechanism of this interaction is not clear.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[See 'Warnings and Precautions' section]*

TARCEVA can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant while being treated with TARCEVA.

Erlotinib has been shown to cause maternal toxicity with associated embryofetal lethality and abortion in rabbits when given at doses that result in plasma drug concentrations of approximately 3 times those in humans (AUCs at 150 mg daily dose). When given during the period of organogenesis to achieve plasma drug concentrations approximately equal to those in humans, based on AUC, there was no increased incidence of embryofetal lethality or abortion in rabbits or rats. However, female rats treated with 30 mg/m^2/day or 60 mg/m^2/day (0.3 or 0.7 times the clinical dose, on a mg/m^2 basis) of erlotinib prior to mating through the first week of pregnancy had an increase in early resorptions that resulted in a decrease in the number of live fetuses.

No teratogenic effects were observed in rabbits or rats dosed with erlotinib during organogenesis at doses up to 600 mg/m^2/day in the rabbit (3 times the plasma drug concentration seen in humans at 150 mg/day) and up to 60 mg/m^2/day in the rat (0.7 times the clinical dose of 150 mg/day on a mg/m^2 basis).

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

Appendix B
Tarceva® Package Insert (cont.)

8.5 Geriatric Use

Maintenance Study

Of the total number of patients participating in the randomized NSCLC Maintenance trial, 66% were less than 65 years of age, and 34% of patients were aged 65 years or older. The hazard ratio for overall survival was 0.78 (95% CI: 0.65, 0.95) in patients less than 65 years of age and 0.88 (95% CI: 0.68, 1.15) in patients who were 65 years or older.

Second/Third Line Study

Of the total number of patients participating in the randomized 2nd/3rd line NSCLC trial, 61% were less than 65 years of age, and 39% of patients were aged 65 years or older. The survival benefit was maintained across both age groups [OS HR = 0.75 (95% CI: 0.6, 0.9) in patients less than 65 years of age, and OS HR = 0.79 (95% CI: 0.6, 1.0) in patients who were 65 years or older].

First-Line Pancreatic Cancer

In the pancreatic cancer study, 52 % of patients were younger than 65 years of age and 48 % were 65 years of age or older. There were no clinically relevant survival differences between the age groups [OS HR = 0.78 (95% CI: 0.6, 1.0) in patients less than 65 years of age, and OS HR = 0.94 (95% CI: 0.7, 1.2) in patients who were 65 years or older]. No meaningful differences in safety or pharmacokinetics were observed between younger and older patients in these studies. Therefore, no dosage adjustments are recommended in elderly patients.

8.6 Gender

Maintenance Study

Of the total number of patients participating in the randomized Maintenance trial, 73% were males and 27% females. There were no clinically relevant differences in safety and efficacy based on gender [OS HR = 0.88 (95% CI: 0.74, 1.05) in males and OS HR = 0.64 (95% CI: 0.46, 0.91) in females].

Second/Third Line Study

Of the total number of patients participating in the randomized 2nd/3rd line NSCLC trial, 65% were males and 35% females. There were no clinically relevant differences in safety and efficacy based on gender [OS HR = 0.76 (95% CI: 0.6, 0.9) in males and OS HR = 0.80 (95% CI: 0.6, 1.1) in females].

First Line Pancreatic Cancer

In the pancreatic cancer study, 51% of patients were males and 49% females. There were no clinically relevant differences in safety and efficacy based on gender [OS HR = 0.74 (95% CI: 0.6, 0.9) in males and OS HR = 1.0 (95% CI: 0.8, 1.3) in females].

8.7 Race

Maintenance Study

In the randomized Maintenance trial, 84% of all patients were Caucasian and 15% were Asian. There were no clinically relevant differences in safety and efficacy based on race [OS HR = 0.86 (95% CI: 0.73, 1.01) in Caucasians and OS HR = 0.66 (95% CI: 0.42, 1.05) in Asians].

Second/Third Line Study

In the randomized 2nd/3rd line NSCLC trial, 78% of all patients were Caucasian and 13% were Asian. There were no clinically relevant differences in safety and efficacy based on race [OS HR = 0.79 (95% CI: 0.6, 1.0) in Caucasians and OS HR = 0.61 (95% CI: 0.4, 1.0) in Asians].

Appendix B
Tarceva® Package Insert (cont.)

First-Line Pancreatic Cancer

In the pancreatic cancer study, 86% of all patients were Caucasian and 8% were Asian. There were no clinically relevant differences in safety and efficacy based on race [OS HR = 0.88 (95% CI: 0.7, 1.1) in Caucasians and OS HR = 0.61 (95% CI: 0.3, 1.3) in Asians].

8.8 Patients with Hepatic Impairment

Patients with hepatic impairment (total bilirubin > ULN or Child Pugh A, B and C) should be closely monitored during therapy with TARCEVA. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN *[see Warnings and Precautions (5.4), Adverse Reactions (6.1, 6.2), and Dosage and Administration (2.3)]*.

In vitro and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver. However, erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.9 Patients with Renal Impairment

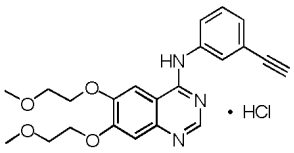
Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

10 OVERDOSAGE

Single oral doses of TARCEVA up to 1,000 mg in healthy subjects and weekly doses up to 1,600 mg in cancer patients have been tolerated. Repeated twice-daily doses of 200 mg single-agent TARCEVA in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, an unacceptable incidence of severe adverse reactions, such as diarrhea, rash, and liver transaminase elevation, may occur above the recommended dose *[see Dosage and Administration (2)]*. In case of suspected overdose, TARCEVA should be withheld and symptomatic treatment instituted.

11 DESCRIPTION

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



Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4.HCl$ and a molecular weight of 429.90. The molecule has a pK_a of 5.42 at 25°C. Erlotinib hydrochloride is very slightly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane.

Aqueous solubility of erlotinib hydrochloride is dependent on pH with increased solubility at a pH of less than 5 due to protonation of the secondary amine. Over the pH range of 1.4 to 9.6, maximal solubility of approximately 0.4 mg/mL occurs at a pH of approximately 2.

TARCEVA tablets for oral administration are available in three dosage strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg and 163.9 mg) equivalent to 25 mg, 100 mg and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow #6 (25 mg only) for product identification.

Appendix B
Tarceva® Package Insert (cont.)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Absorption and Distribution:

Erlotinib is about 60% absorbed after oral administration and its bioavailability is substantially increased by food to almost 100%. Peak plasma levels occur 4 hours after dosing. The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Co-administration of TARCEVA with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure [AUC] and maximum concentration [C_{max}] by 46% and 61% respectively. When TARCEVA was administered 2 hours following a 300 mg dose of ranitidine, an H_2 receptor antagonist, the erlotinib AUC was reduced by 33% and C_{max} by 54%. When TARCEVA was administered with ranitidine 150 mg twice daily (at least 10 h after the previous ranitidine evening dose and 2 h before the ranitidine morning dose), the erlotinib AUC and C_{max} decreased by 15% and 17% respectively *[see Drug Interactions (7)]*.

Following absorption, erlotinib is approximately 93% protein bound to plasma albumin and alpha-1 acid glycoprotein (AAG). Erlotinib has an apparent volume of distribution of 232 liters.

Metabolism and Excretion:

A population pharmacokinetic analysis in 591 patients receiving the single-agent TARCEVA $2^{nd}/3^{rd}$ line regimen showed a median half-life of 36.2 hours. Time to reach steady state plasma concentration would therefore be 7 – 8 days. No significant relationships of clearance to covariates of patient age, body weight or gender were observed. Smokers had a 24% higher rate of erlotinib clearance.

An additional population pharmacokinetic analysis was conducted in 291 NSCLC patients administered single-agent erlotinib as maintenance treatment. This analysis demonstrated that covariates affecting erlotinib clearance in this patient population were similar to those seen in the prior single-agent pharmacokinetic analysis. No new covariate effects were identified.

A third population pharmacokinetic analysis was conducted that incorporated erlotinib data from 204 pancreatic cancer patients who received erlotinib plus gemcitabine. Similar results were observed to those seen in the prior single-agent pharmacokinetic analysis. No new covariate effects were identified. Co-administration of gemcitabine had no effect on erlotinib plasma clearance.

In vitro assays of cytochrome P450 metabolism showed that erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic isoform CYP1A1. Following a 100 mg oral dose, 91% of the dose was recovered: 83% in feces (1% of the dose as intact parent) and 8% in urine (0.3% of the dose as intact parent).

Cigarette smoking reduces erlotinib exposure. In the Phase 3 NSCLC trial, current smokers achieved erlotinib steady-state trough plasma concentrations which were approximately 2-fold less than the former smokers or patients who had never smoked. This effect was accompanied by a 24% increase in apparent erlotinib plasma clearance. In a separate study which evaluated the single-dose pharmacokinetics of erlotinib in healthy volunteers, current smokers cleared the drug faster than former smokers or volunteers who had never smoked. The $AUC_{0\text{-infinity}}$ in smokers was about 1/3 to 1/2 of that in never/former smokers. In another study which was conducted in NSCLC patients (N=35) who were current smokers, pharmacokinetic analyses at steady-state indicated a dose-proportional increase in erlotinib exposure when the TARCEVA dose was increased from 150 mg to 300 mg. However, the exact dose to be recommended for patients who currently smoke is unknown *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

Special Populations:

Patients with Hepatic Impairment

Patients with hepatic impairment (total bilirubin > ULN or Child Pugh A, B and C) should be closely monitored during therapy with TARCEVA. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN *[see Warnings and Precautions (5.4), Adverse Reactions (6.1, 6.2), and Dosage and Administration (2.3)]*.

Appendix B
Tarceva® Package Insert (cont.)

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

Patients with Renal Impairment

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in mice and rats orally, at erlotinib doses up to 60 mg/kg/day in mice, 5 mg/kg/day in female rats, and 10 mg/kg/day in male rats. The studies were negative for carcinogenic findings. Exposure in mice at the highest dose tested was approximately 10-fold the exposure in humans at the erlotinib dose of 150 mg/day. The highest doses evaluated in rats resulted in exposures that were 2-fold of human values in male rats and similar, but slightly lower than human values in female rats.

Erlotinib has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration and mammalian cell mutation) and *in vivo* mouse bone marrow micronucleus test and did not cause genetic damage.

Erlotinib did not impair fertility in either male or female rats.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer (NSCLC) – TARCEVA Monotherapy Administered as Maintenance Treatment

The efficacy and safety of TARCEVA as maintenance treatment of NSCLC were demonstrated in a randomized, double-blind, placebo-controlled trial conducted in 26 countries, in 889 patients with locally advanced or metastatic NSCLC whose disease did not progress during first line platinum-based chemotherapy. Patients were randomized 1:1 to receive TARCEVA 150 mg or placebo orally once daily (438 TARCEVA, 451 placebo) until disease progression or unacceptable toxicity. The primary objective of the study was to determine if the administration of TARCEVA after standard platinum-based chemotherapy in the treatment of NSCLC resulted in improved progression free survival (PFS) when compared with placebo, in all patients or in patients with EGFR immunohistochemistry (IHC) positive tumors.

Demographic characteristics were balanced between the two treatment groups (Table 5).

Table 5: Demographic and Disease Characteristics:

	TARCEVA N=438		PLACEBO N=451	
Characteristics	**N**	**(%)**	**N**	**(%)**
Gender				
Female	117	(27%)	113	(25%)
Male	321	(73%)	338	(75%)
Age (years)				
≥65 Years	148	(34%)	151	(33%)
< 65 Years	290	(66%)	300	(67%)
Stage of NSCLC				
Unresectable Stage IIIB	116	(26%)	109	(24%)

Appendix B
Tarceva® Package Insert (cont.)

	TARCEVA N=438		PLACEBO N=451	
Stage IV	322	(74%)	342	(76%)
Race				
Caucasian	370	(84%)	376	(83%)
Black	3	(<1%)	1	(<1%)
Asian	62	(14%)	69	(15%)
Other	3	(<1%)	5	(1%)
ECOG Performance Status at Baseline				
0	135	(31%)	145	(32%)
1	303	(69%)	306	(68%)
EGFR IHC				
Positive	308	(70%)	313	(69%)
Negative	62	(14%)	59	(13%)
Indeterminate	16	(4%)	24	(5%)
Missing	52	(12%)	55	(12%)
Histology				
Squamous	166	(38%)	194	(43%)
Adenocarcinoma including Bronchioloaveolar	205	(47%)	198	(44%)
Large Cell	21	(5%)	24	(5%)
Other	46	(11%)	35	(8%)
Smoking Status				
Current Smoker	239	(55%)	254	(56%)
Never Smoked	77	(18%)	75	(17%)
Past Smoker	122	(28%)	122	(27%)
Smoking status: Current smoker = smoker at time of randomization or stopped within 1 year prior to randomization.				

Progression free survival (PFS) and overall survival (OS) were evaluated in the intent-to-treat (ITT) population. The results of the study are shown in Table 6.

Table 6: Efficacy Results: (ITT Population)

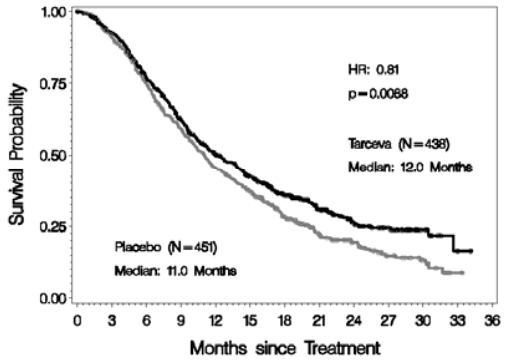
	Median in Months (95% CI)		Hazard Ratio (1) (95% CI)	p-value (2)
	TARCEVA 150 mg N = 438	Placebo N=451		
Progression-Free Survival based on investigator's assessment	2.8 (2.8, 3.1)	2.6 (1.9, 2.7)	0.71 (0.62, 0.82)	p < 0.0001
Overall Survival	12.0 (10.6, 13.9)	11.0 (9.9,12.1)	0.81 (0.70, 0.95)	0.0088

(1) Univariate Cox regression model

(2) Unstratified log-rank test.

Figure 1 depicts the Kaplan Meier Curves for Overall Survival (ITT Population).

Figure 1: Kaplan–Meier Curve for Overall Survival of Patients by Treatment Group



Note: HR is from a univariate Cox regression model.

The PFS and OS Hazard Ratios, respectively, in patients with EGFR IHC-positive tumors were 0.69 (95% CI: 0.58, 0.82) and 0.77 (95% CI: 0.64, 0.93). The PFS and OS Hazard Ratios in patients with IHC-negative tumors were 0.77 (95% CI: 0.51, 1.14) and 0.91 (95% CI: 0.59, 1.38), respectively.

Patients with adenocarcinoma had an OS Hazard Ratio of 0.77 (95% CI: 0.61, 0.97) and patients with squamous histology had an OS Hazard Ratio of 0.86 (95% CI: 0.68, 1.10).

14.2 NSCLC – Second/Third Line Study

The efficacy and safety of single-agent TARCEVA was assessed in a randomized, double blind, placebo-controlled trial in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomized 2:1 to receive TARCEVA 150 mg or placebo (488 Tarceva, 243 placebo) orally once daily until disease progression or unacceptable toxicity. Study endpoints included overall survival, response rate, and progression-free survival (PFS). Duration of response was also examined. The primary endpoint was survival. The study was conducted in 17 countries.

Table 7 summarizes the demographic and disease characteristics of the study population. Demographic characteristics were well balanced between the two treatment groups. About two-thirds of the patients were male. Approximately one-fourth had a baseline ECOG performance status (PS) of 2, and 9% had a baseline ECOG PS of 3. Fifty percent of the patients had received only one prior regimen of chemotherapy. About three quarters of these patients were known to have smoked at some time.

Table 7: Demographic and Disease Characteristics

	TARCEVA (N = 488)		Placebo (N = 243)	
Characteristics	**n**	**(%)**	**n**	**(%)**
Gender				
Female	173	(35)	83	(34)
Male	315	(65)	160	(66)

Appendix B
Tarceva® Package Insert (cont.)

	TARCEVA (N = 488)		Placebo (N = 243)	
Age (years)				
< 65	299	(61)	153	(63)
≥ 65	189	(39)	90	(37)
Race				
Caucasian	379	(78)	188	(77)
Black	18	(4)	12	(5)
Asian	63	(13)	28	(12)
Other	28	(6)	15	(6)
ECOG Performance Status at Baseline*				
0	64	(13)	34	(14)
1	256	(52)	132	(54)
2	126	(26)	56	(23)
3	42	(9)	21	(9)
Weight Loss in Previous 6 Months				
< 5%	320	(66)	166	(68)
5 – 10%	96	(20)	36	(15)
> 10%	52	(11)	29	(12)
Unknown	20	(4)	12	(5)
Smoking History				
Never Smoked	104	(21)	42	(17)
Current or Ex-smoker	358	(73)	187	(77)
Unknown	26	(5)	14	(6)
Histological Classification				
Adenocarcinoma	246	(50)	119	(49)
Squamous	144	(30)	78	(32)
Undifferentiated Large Cell	41	(8)	23	(9)
Mixed Non-Small Cell	11	(2)	2	(<1)
Other	46	(9)	21	(9)
Time from Initial Diagnosis to Randomization (Months)				
< 6	63	(13)	34	(14)
6 – 12	157	(32)	85	(35)

Appendix B
Tarceva® Package Insert (cont.)

	TARCEVA (N = 488)		Placebo (N = 243)	
> 12	268	(55)	124	(51)
Best Response to Prior Therapy at Baseline*				
CR/PR	196	(40)	96	(40)
PD	101	(21)	51	(21)
SD	191	(39)	96	(40)
Number of Prior Regimens at Baseline*				
1	243	(50)	121	(50)
2	238	(49)	119	(49)
3	7	(1)	3	(1)
Exposure to Prior Platinum at Baseline*				
Yes	454	(93)	224	(92)
No	34	(7)	19	(8)

* Stratification factor as documented at baseline; distribution differs slightly from values reported at time of randomization.

The results of the study are shown in Table 8.

Table 8: Efficacy Results

	TARCEVA	Placebo	Hazard Ratio (1)	95% CI	p-value
Survival	Median 6.7 mo	Median 4.7 mo	0.73	0.61 – 0.86	<0.001 (2)
1-year Survival	31.2%	21.5%			
Progression-Free Survival	Median 9.9 wk	Median 7.9 wk	0.59	0.50 – 0.70	<0.001 (2)
Tumor Response (CR+PR)	8.9%	0.9%			<0.001 (3)
Response Duration	Median 34.3 wk	Median 15.9 wk			

(1) Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

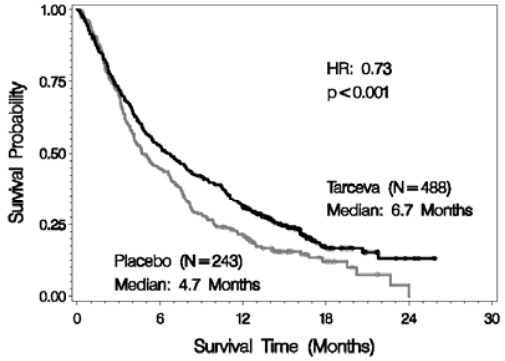
(2) Two-sided Log-Rank test stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

(3) Two-sided Fisher's exact test

Survival was evaluated in the intent-to-treat population. Figure 2 depicts the Kaplan-Meier curves for overall survival. The primary survival and PFS analyses were two-sided Log-Rank tests stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

Appendix B
Tarceva® Package Insert (cont.)

Figure 2: Kaplan–Meier Curve for Overall Survival of Patients by Treatment Group



Note: HR is from Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy. P-value is from two-sided Log-Rank test stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

14.3 NSCLC - TARCEVA Administered Concurrently with Chemotherapy

Results from two, multicenter, placebo-controlled, randomized, trials in over 1000 patients conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel (TARCEVA, N = 526) or gemcitabine and cisplatin (TARCEVA, N = 580)].

14.4 Pancreatic Cancer - TARCEVA Administered Concurrently with Gemcitabine

The efficacy and safety of TARCEVA in combination with gemcitabine as a first-line treatment was assessed in a randomized, double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomized 1:1 to receive TARCEVA (100 mg or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m^2, Cycle 1 - Days 1, 8, 15, 22, 29, 36 and 43 of an 8 week cycle; Cycle 2 and subsequent cycles - Days 1, 8 and 15 of a 4 week cycle [the approved dose and schedule for pancreatic cancer, see the gemcitabine package insert]). TARCEVA or placebo was taken orally once daily until disease progression or unacceptable toxicity. The primary endpoint was survival. Secondary endpoints included response rate, and progression-free survival (PFS). Duration of response was also examined. The study was conducted in 18 countries. A total of 285 patients were randomized to receive gemcitabine plus TARCEVA (261 patients in the 100 mg cohort and 24 patients in the 150 mg cohort) and 284 patients were randomized to receive gemcitabine plus placebo (260 patients in the 100 mg cohort and 24 patients in the 150 mg cohort). Too few patients were treated in the 150 mg cohort to draw conclusions.

Table 9 summarizes the demographic and disease characteristics of the study population that was randomized to receive 100 mg of TARCEVA plus gemcitabine or placebo plus gemcitabine. Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups, except for a slightly larger proportion of females in the TARCEVA arm (51%) compared with the placebo arm (44%). The median time from initial diagnosis to randomization was approximately 1.0 month. Most patients presented with metastatic disease at study entry as the initial manifestation of pancreatic cancer.

Appendix B
Tarceva® Package Insert (cont.)

Table 9: Demographic and Disease Characteristics: 100 mg Cohort

	TARCEVA+ Gemcitabine (N=261)		Placebo + Gemcitabine (N=260)	
Characteristics	**N**	**(%)**	**N**	**(%)**
Gender				
Female	134	(51)	114	(44)
Male	127	(49)	146	(56)
Age (Years)				
<65	136	(52)	138	(53)
≥65	125	(48)	122	(47)
Race				
Caucasian	225	(86)	231	(89)
Black	8	(3)	5	(2)
Asian	20	(8)	14	(5)
Other	8	(3)	10	(3)
ECOG Performance Status*				
0	82	(31)	83	(32)
1	134	(51)	132	(51)
2	44	(17)	45	(17)
Unknown*	1	(<1)	0	(0)
Disease Status at Baseline**				
Locally Advanced	61	(23)	63	(24)
Distant Metastasis	200	(77)	197	(76)

*Unknown includes responses of 'Unknown' and missing.

**Stratification factor as documented at baseline; distribution differs slightly from values reported at time of randomization.

The results of the study are shown in Table 10.

Appendix B
Tarceva® Package Insert (cont.)

Table 10: Efficacy Results: 100 mg Cohort

	TARCEVA + Gemcitabine	Placebo+ Gemcitabine	Hazard Ratio (1)	95% CI	p-value
Survival	Median 6.4 mo 250 deaths	Median 6.0 mo 254 deaths	0.81	0.68 – 0.97	0.028 (2)
1-year Survival	23.8%	19.4%			
Progression-Free Survival	Median 3.8 mo 225 events	Median 3.5 mo 232 events	0.76	0.64 – 0.92	0.006 (2)
Tumor Response (CR+PR)	8.6%	7.9%			0.87 (3)
Response Duration	Median 23.9 wk	Median 23.3 wk			

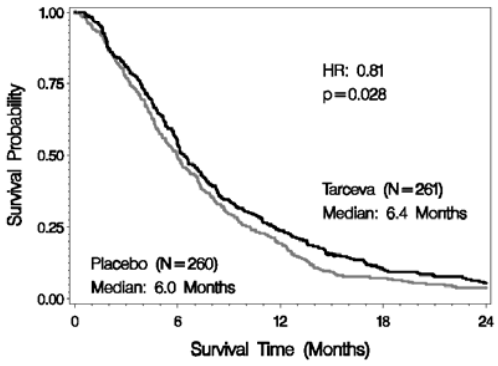
(1) Cox regression model with the following covariates: ECOG performance status, and extent of disease.

(2) Two-sided Log-Rank test stratified by ECOG performance status and extent of disease.

(3) Two-sided Fisher's exact test.

Survival was evaluated in the intent-to-treat population. Figure 3 depicts the Kaplan-Meier curves for overall survival in the 100 mg cohort. The primary survival and PFS analyses were two-sided Log-Rank tests stratified by ECOG performance status and extent of disease.

Figure 3: Kaplan – Meier Curve for Overall Survival: 100 mg Cohort



Note: HR is from Cox regression model with the following covariates: ECOG performance status and extent of disease. P-value is from two-sided Log-Rank test stratified by ECOG performance status and extent of disease.

16 HOW SUPPLIED/STORAGE AND HANDLING

25 mg Tablets

Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side; supplied in:

Bottles of 30: NDC 50242-062-01

Appendix B
Tarceva® Package Insert (cont.)

100 mg Tablets
Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side; supplied in:
Bottles of 30: NDC 50242-063-01

150 mg Tablets
Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side; supplied in:
Bottles of 30: NDC 50242-064-01

Store at 25°C (77°F); excursions permitted to 15° – 30°C (59° – 86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

If the following signs or symptoms occur, patients should be advised to seek medical advice promptly *[see Warnings and Precautions (5), Adverse Reactions (6) and Dosage and Administration (2.3)]*.

- Onset or worsening of skin rash
- Severe or persistent diarrhea, nausea, anorexia, or vomiting
- Onset or worsening of unexplained shortness of breath or cough
- Eye irritation

Given that skin reactions are anticipated when taking TARCEVA, proactive intervention may include alcohol-free emollient cream and use of sunscreen or avoidance of sun exposure *[see Adverse Reactions (6.1)*.] The management of rash should be discussed with the patient. This may include topical corticosteroids or antibiotics with anti-inflammatory properties. These approaches were used in the NSCLC and pancreatic pivotal clinical trials. Acne preparations with drying properties may aggravate the dry skin and erythema. Treatment of rash has not been formally studied and should be based on rash severity.

Women of childbearing potential should be advised to avoid becoming pregnant while taking TARCEVA *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.1)]*.

Smokers should be advised to stop smoking while taking TARCEVA as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking *[see Clinical Pharmacology (12.3)]*.

Appendix B
Tarceva® Package Insert (cont.)

Copy from GRASS PID2012-02130

Manufactured for:

OSI Pharmaceuticals, LLC, Farmingdale, NY 11735
an affiliate of Astellas Pharma US, Inc.

Manufactured by:

Kremers Urban Pharmaceuticals, Inc., Seymour, IN 47274

Distributed by:

Genentech USA, Inc., A Member of the Roche Group 1 DNA Way, South San Francisco, CA 94080-4990

For further information please call 1-877-TARCEVA (1-877-827-2382).

12D031-TAR-WPI

Appendix C
Final Study Results

Final Study Results

A Phase III, multicenter, placebo-controlled, double-blind, randomized, clinical trial to evaluate the efficacy of bevacizumab (Avastin®) in combination with erlotinib (Tarceva®) compared with erlotinib alone for treatment of advanced non–small cell lung cancer (NSCLC) after failure of standard first-line chemotherapy (BETA).

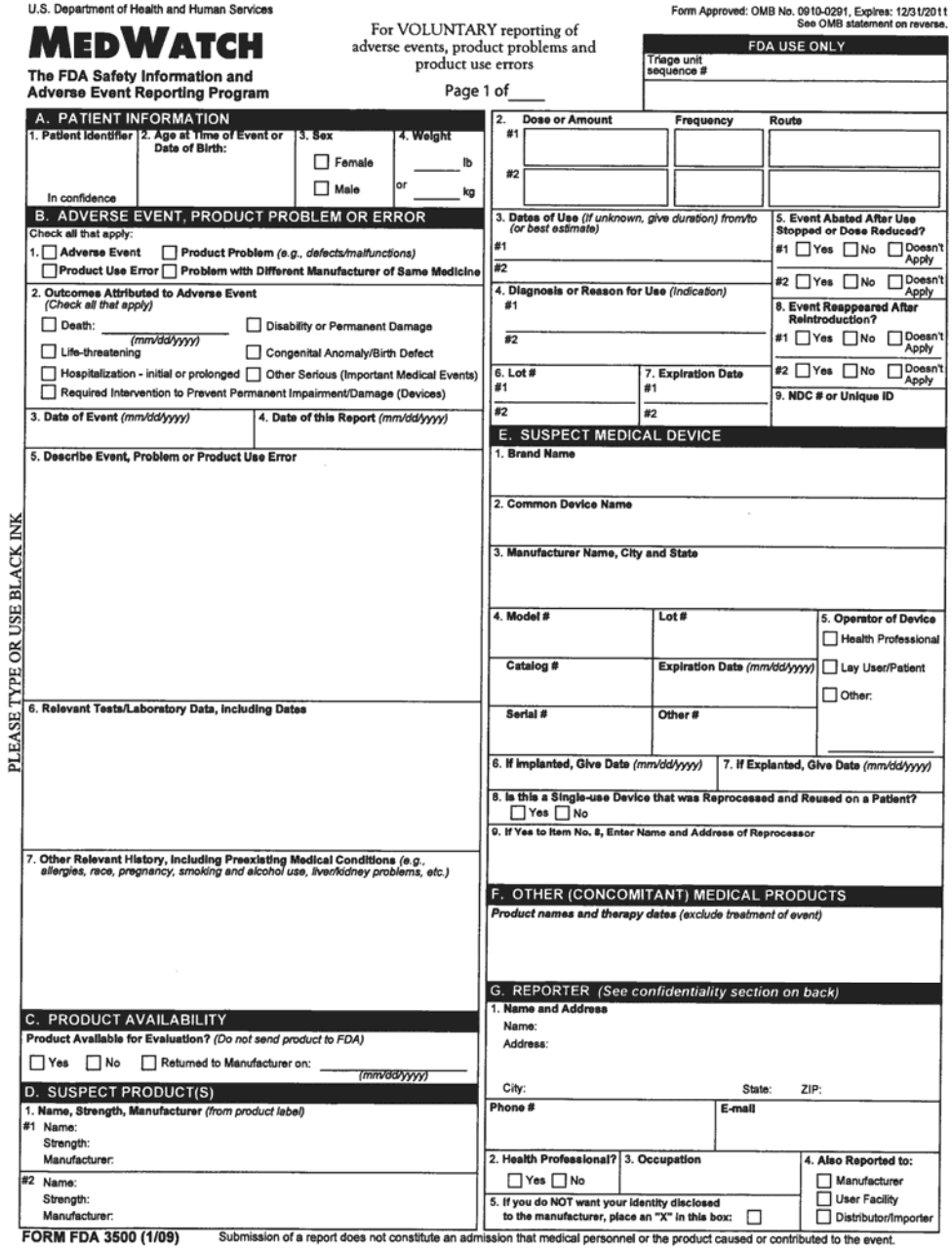
Authors: J Hainsworth[1], M Lin[2], P O'Connor[2], and R Herbst[3] for the BETA Lung Investigators (1 Sarah Cannon Research Institute, Nashville TN, 2 Genentech, Inc., San Francisco, CA, 3 MD Anderson Cancer Center, Houston TX)

Background: Bevacizumab (B) with chemotherapy and erlotinib (E) monotherapy have demonstrated a survival benefit in the treatment of patients (pts) with advanced NSCLC (Sandler et al. NEJM 2006; Shepherd et al. NEJM 2005). Randomized Phase II data supported the hypothesis that combining B + E might improve efficacy, with acceptable safety (Herbst et al. JCO 2007).

Methods: Patients with advanced NSCLC who progressed during or after first-line therapy were enrolled. The primary endpoint of the trial was overall survival (OS). Secondary endpoints included PFS and ORR. Eligible patients were B appropriate, including a group with treated brain metastases, squamous cell disease at low risk for bleeding, and those requiring anticoagulation. Previous anti-angiogenisis or epidermal growth factor receptor (EGFR) targeted therapy was not allowed. Patients were randomized (1:1) to B + E or E + placebo (P). E dosing was 150 mg daily. B/P dosing was 15 mg/kg intravenous every 3 weeks. Responses were assessed every 6 weeks until Week 24 and every 12 weeks thereafter. Treatment continued until disease progression or unacceptable toxicity.

Results: 636 patients were enrolled from June 2005 to April 2008. The final analysis was conducted after 418 deaths were recorded. Median OS was 9.3 mos (B + E) vs. 9.2 months (E+P), p = 0.75, HR=0.97(95% CI: 0.80 -1.18). Median PFS was 3.4 mos (B+E) vs. 1.7 mos (E+P), p<0.0001; HR = 0.62 (95%CI: 0.52-0.75). ORR was 12.6% (B+E) vs.6.2% (E+P), p=0.006. The safety profile for B+E was consistent with known profiles for B and E and will be described further at presentation. Conclusions: The addition of B to E in the BETA lung study was not associated with an improvement overall survival. However, B + E doubled PFS and ORR, providing clear evidence of clinical activity.

Appendix D
MedWatch Form FDA 3500



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of ____

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — _____ lb or _____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☐ Disability or Permanent Damage
☐ Life-threatening
☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*
4. Date of this Report *(mm/dd/yyyy)*

5. Describe Event, Problem or Product Use Error

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Name:
Strength:
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount / Frequency / Route
#1
#2

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1
#2

4. Diagnosis or Reason for Use *(Indication)*
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
#1
#2

7. Expiration Date
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model #
Catalog #
Serial #
Lot #
Expiration Date *(mm/dd/yyyy)*
Other #
5. Operator of Device
☐ Health Professional
☐ Lay User/Patient
☐ Other: _____
6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
Name:
Address:
City: State: ZIP:
Phone #
E-mail
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to:
☐ Manufacturer
☐ User Facility
☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Appendix D
MedWatch Form FDA 3500 (cont'd)

ADVICE ABOUT VOLUNTARY REPORTING

Detailed instructions available at: http://www.fda.gov/medwatch/report/consumer/instruct.htm

Report adverse events, product problems or product use errors with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Combination products *(medication & medical devices)*
- Human cells, tissues, and cellular and tissue-based products
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures (product didn't work)

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization - initial or prolonged
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (devices)
- Other serious (important medical events)

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section D for all products except medical devices
- Attach additional pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Other methods of reporting:

- 1-800-FDA-0178 - To FAX report
- 1-800-FDA-1088 - To report by phone
- www.fda.gov/medwatch/report.htm - To report online

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

If your report involves a serious adverse event with a vaccine, call 1-800-822-7967 to report.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

-Fold Here-

-Fold Here-

The public reporting burden for this collection of information has been estimated to average 36 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

Please DO NOT RETURN this form to this address.

OMB statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (1/09) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

Appendix D
MedWatch Form FDA 3500 (cont'd)

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

(CONTINUATION PAGE)

For VOLUNTARY reporting of adverse events and product problems

Page 3 of ____

B.5. Describe Event or Problem *(continued)*
B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*
B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)* *(continued)*
F. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)* *(continued)*

Appendix D
MedWatch Form FDA 3500 (cont'd)

General Instructions for Completing the MedWatch Form FDA 3500

For use by health professionals and consumers for **VOLUNTARY** reporting of adverse events, product use errors and product quality problems with:

- Drugs
- Biologics (including blood components, blood derivatives, allergenics, human cells, tissues, and cellular and tissue-based products (HCT/Ps)
- Medical devices (including *in-vitro* diagnostics)
- Combination products (e.g. drug-device, biologic-device)
- Special nutritional products (dietary supplements, infant formulas, medical foods)
- Cosmetics

Adverse events involving **vaccines** should be reported to the Vaccine Adverse Event Reporting System (VAERS), http://vaers.hhs.gov/pdf/vaers_form.pdf Adverse events involving **investigational (study) drugs, such as those relating to Investigational New Drug (IND) applications**, should be reported as required in the study protocol and sent to the address and contact person listed in the study protocol. They should generally not be submitted to FDA MedWatch as voluntary reports.

Note for consumers: If possible, please take the 3500 form to your health professional (e.g., doctor or pharmacist) so that information based on your medical record that can help in the evaluation of your report will be provided. If, for whatever reason, you do not wish to have your health professional fill out the form, you are welcome to do so yourself.

GENERAL INSTRUCTIONS

- Please make sure that all entries are either typed, printed in a font no smaller than 8 point, or written using black ink.
- Please complete all sections that apply to your report.
- Dates should be entered as mm/dd/yyyy (e.g., June 3, 2005 = 06/03/2005). If exact dates are unknown, please provide the best estimate (see block **B3**).
- For narrative entries, if the fields do not provide adequate space, attach additional pages as needed.
- If attaching additional pages, please do the following:
  - Identify all attached pages as Page __ of __
  - Indicate the appropriate section and block number next to the narrative continuation.
  - Include the phrase continued at the end of each field that has additional information continued on to another page.
- **Section D,** Suspect product(s), should be used to report on special nutritional products and cosmetics as well as drugs or biologics, including human cells, tissues, and cellular and tissue-based products (HCT/Ps).
- If your report involves a serious adverse event with a device and it occurred in a facility other than a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Appendix D
MedWatch Form FDA 3500 (cont'd)

SECTION A: PATIENT INFORMATION

Complete a separate form for each patient, unless the report involves a medical device where multiple patients were adversely affected through the use of the same device. In that case, please indicate the number of patients in block **B5** (Describe event or problem) and complete Section A and blocks **B2**, **B5**, **B6**, **B7**, and **F** for each patient. Enter the corresponding patient identifier in block **A1** for each patient involved in the event.

Parent-child/fetus report(s) are those cases in which either a fetus/breast-feeding infant or the mother, or both have an adverse event that is possibly associated with a product administered to the mother during pregnancy. Several general principles are used for filing these reports:

- If there has been no event affecting the child/fetus, report only on the parent.
- For those cases describing fetal death, miscarriage or abortion, report the parent as the patient in the report.
- When only the child/fetus has an adverse reaction/ event (other than fetal death, miscarriage or abortion), the information provided in **Section A** applies to the child/fetus. However, the information in **Section D** would apply to the parent who was the source of exposure to the product.
- When a newborn baby is found to have a birth defect/congenital anomaly that the initial reporter considers possibly associated with a product administered to the mother during pregnancy, the patient is the newborn baby.
- If both the parent and the child/fetus have adverse events, separate reports should be submitted for each patient.

A1: Patient Identifier

Please provide the patient's initials or some other type of identifier that will allow you, the reporter, to readily locate the case if you are contacted for more information. Do not use the patient's name or social security number.

The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

If no patient was involved (such as may be the case with a product problem), enter none.

A2: Age at Time of Event or Date of Birth

Provide the most precise information available. Enter the patient's birth date, if known, or the patient's age at the time of event onset. For age, indicate time units used (e.g., years, months, days):

- If the patient is 3 years or older, use years (e.g., 4 years).
- If the patient is less than 3 years old, use month (e.g., 24 months).
- If the patient is less than 1 month old, use days (e.g., 5 days).
- Provide the best estimate if exact age is unknown.

A3: Sex

Enter the patient's gender. If the adverse event is a congenital anomaly/birth defect, report the sex of the child.

A4: Weight

Indicate whether the weight is in pounds (lb) or kilograms (kg). Make a best estimate if exact weight is unknown.

Appendix D
MedWatch Form FDA 3500 (cont'd)

SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR

B1: Adverse Event, Product Problem, Product Use Error, or Problem with Different Manufacturer of Same Medicine.

Choose the appropriate box(es). If a product problem may have caused or contributed to the adverse event, check both boxes.

Adverse event: Any incident where the use of a medication (drug or biologic, including HCT/P), at any dose, a medical device (including *in-vitro* diagnostics) or a special nutritional product (e.g., dietary supplement, infant formula or medical food) is suspected to have resulted in an adverse outcome in a patient.

To report, it is not necessary to be certain of a cause/effect relationship between the adverse event and the use of the medical product(s) in question. Suspicion of an association is sufficient reason to report. Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Please limit your submissions to those events that are serious. An event is classified as serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly/Birth Defect
- Required Medical or Surgical Intervention to Prevent Permanent Impairment or Damage (Devices)
- Other Serious (Important Medical Events)

Please see instructions for block **B2** for further information on each of these criteria.

Product problem (e.g., defects/malfunctions): Any report regarding the quality, performance, or safety of any medication, medical device or special nutritional product. In addition, please select this category when reporting device malfunctions that could lead to a death or serious injury if the malfunction were to recur. Product problems include, but are not limited to, such concerns as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Therapeutic failures (product didn't work)
- Product confusion (caused by name, labeling, design or packaging)
- Suspected superpotent or subpotent medication
- Labeling problems caused by printing errors/omissions

Product Use Error:

Medication Use Error: Any report of a medication error regardless of patient involvement or outcome. Also report circumstances or events that have the capacity to cause error (e.g., similar product appearance, similar packaging and labeling, sound-alike/look-alike names, etc.).

Medication errors can and do originate in all stages of the medication use system, which includes selecting and procuring drugs, prescribing, preparing and dispensing, administering and monitoring. A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use."

Medical Device Use Error: Health care professionals, patients, and consumers can unintentionally cause harm to patients or to themselves when using medical devices. These problems can often arise due to problems with the design of the medical device or the manner in which the device is used. Often, use errors are caught and prevented before they can do harm (close call). Report use errors regardless of patient involvement or outcome. Also report circumstances or events that could cause use errors. Medical device use errors usually occur for one or more of the following reasons:

- Users expect devices to operate differently than they do.
- Product use is inconsistent with use's expectations or intuition.
- Product use requires physical, perceptual, or cognitive abilities that exceed those of the user.
- Devices are used in ways not anticipated by the manufacturer.
- Product labeling or packaging is confusing or inadequate.
- The environment adversely affects or influences device use.

Problem with Different Manufacturer of Same Medicine: Any incident, to include, but not be limited to, differences in noted therapeutic response, suspected to have resulted from a switch, or change, from one manufacturer to another manufacturer of the **same** medicine or drug product. This could be changes from a brand name drug product to a generic manufacturer's same product, or from a generic manufacturer's product to the same

(continued on next page)

Appendix D
MedWatch Form FDA 3500 (cont'd)

SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR *(continued)*

product as supplied by a different generic manufacturer, or from a generic manufacturer's product to a brand name manufacturer of the same product. In order to fully evaluate the incident, please include in **Section B5**, if available, specific information relative to the switch between different manufacturers of the same medicine, to include, but not be limited to, the names of the manufacturers, length of treatment on each manufacturer's product, product strength, and any relevant clinical data.

B2: Outcomes Attributed to Adverse Event: Indicate all that apply to the reported event:

Death: Check ony if you suspect that the death was an outcome of the adverse event, and include the date if known.

Do not check if:

- The patient died while using a medical product, but there was no suspected association between the death and the use of the product
- A fetus is aborted because of a congenital anomaly (birth defect), or is miscarried

Life-threatening: Check if suspected that:

- The patient was at substantial risk of dying at the time of the adverse event, or
- Use or continued use of the device or other medical product might have resulted in the death of the patient

Hospitalization (initial or prolonged): Check if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Do not check if:

- A patient in the hospital received a medical product and subsequently developed an otherwise nonserious adverse event, unless the adverse event prolonged the hospital stay

Do check if:

- A patient is admitted to the hospital for one or more days, even if released on the same day
- An emergency room visit results in admission to the hospital. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious (medically important event)

Disability or Permanent Damage: Check if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions. Such would be the case if the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect: Check if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices): Check if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events): Check when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

B3: Date of Event

Provide the actual or best estimate of the date of first onset of the adverse event. If day is unknown, month and year are acceptable. If day and month are unknown, year is acceptable.

- When a newborn baby is found to have a congenital anomaly, the event onset date is the date of birth of the child.
- When a fetus is aborted because of a congenital anomaly, or is miscarried, the event onset date is the date pregnancy is terminated.
- If information is available as to time during pregnancy when exposure occurred, indicate that information in narrative block **B5**.

B4: Date of this Report

The date the report is filled out.

B5: Describe Event, Problem or Product Use Error

For an **adverse event:**

Describe the event in detail, including a description of what happened and a summary of all relevant clinical information (medical status prior to the event; signs and/or symptoms; differential diagnosis for the event in question; clinical course; treatment; outcome, etc.). If available and if relevant, include synopses of any office visit notes or the hospital discharge summary. To save time and space (and if permitted by your institution), please attach copies of these records with any confidential information deleted. **Do not identify any patient, physician, or institution by name. The reporter's identity should be provided in full in Section G.**

(continued on next page)

Appendix D
MedWatch Form FDA 3500 (cont'd)

SECTION B: ADVERSE EVENT, PRODUCT PROBLEM, PRODUCT USE ERROR *(continued)*

Information as to any environmental conditions that may have influenced the event should be included, particularly when (but not exclusive to) reporting about a device.

- Results of relevant tests and laboratory data should be entered in block **B6**. (See instructions for **B6**.)
- Preexisting medical conditions and other relevant history belong in block **B7**. Be as complete as possible, including time courses for preexisting diagnoses (see instructions for **B7**).

If it is determined that reuse of a medical device labeled for single use may have caused or contributed to an adverse patient outcome, please report in block **B5** the facts of the incident and the perceived contribution of reuse to the occurrence.

For a product problem: Describe the problem (quality, performance, or safety concern) in sufficient detail so that the circumstances surrounding the defect or malfunction of the medical product can be understood.

- If available, the results of any evaluation of a malfunctioning device and, if known, any relevant maintenance/service information should be included in this section.
- For a medication or special nutritional product problem, please indicate if you have retained a sample that would be available to FDA.

For a product use error: Describe the sequence of events leading up to the error in sufficient detail so that the circumstances surrounding the error can be understood.

- **For Medication Use Errors:** Include a description of the error, type of staff involved, work environment in which the error occurred, indicate causes or contributing factors to the error, location of the error, names of the products involved (including the trade (proprietary) and established (proper) name), manufacturer, dosage form, strength, concentration, and type and size of container.
- **For Medical Device Use Errors:** Report circumstances or events that could cause use errors. Medical device use errors usually occur for one or more of the following reasons:
  - Users expect devices to operate differently than they do.
  - Product use is inconsistent with user's expectations or intuition.
  - Product use requires physical, perceptual, or cognitive abilities that exceed those of the user.
  - Devices are used in ways not anticipated by the manufacturer.
  - Product labeling or packaging is confusing or inadequate.
  - The environment adversely affects or influences device use.

For a problem with a different manufacturer of the same medicine:

Please include specific information relative to the switch between different manufacturers of the same medicine, to include, but not be limited to, the names of the manufacturers, length of treatment on each manufacturer's product, product strength, and any relevant clinical data.

B6: Relevant Tests/Laboratory Data, Including Dates

Please provide all appropriate information, including relevant negative test and laboratory findings, in order to most completely convey how the medical work-up/assessment led to strong consideration of medical product-induced disease as etiology for clinical status, as other differential diagnostic considerations were being eliminated.

Please include:

- Any relevant baseline laboratory data prior to the administration or use of the medical product
- All laboratory data used in diagnosing the event
- Any available laboratory data/engineering analyses (for devices) that provide further information on the course of the event

If available, please include:

- Any pre- and post-event medication levels and dates (if applicable)
- Synopses of any relevant autopsy, pathology, engineering, or lab reports

If preferred, copies of any reports may be submitted as attachments, with all confidential information deleted. **Do not identify any patient, physician or institution by name.** The initial reporter's identity should be provided in full in **Section G.**

B7: Other Relevant History, Including Preexisting Medical Conditions

Knowledge of other risk factors can help in the evaluation of a reported adverse event. If available, provide information on:

- **Other known conditions in the patient, e.g.,**
  - Hypertension (high blood pressure)
  - Diabetes mellitus
  - Liver or kidney problems
- **Significant history**
  - Race
  - Allergies
  - Pregnancy history
  - Smoking and alcohol use, drug abuse
  - Setting

Appendix D
MedWatch Form FDA 3500 (cont'd)

SECTION C: PRODUCT AVAILABILITY

Product available for evaluation? (Do not send the product to FDA.)
To evaluate a reported problem with a medical product, it is often critical to be able to examine the product. Please indicate whether the product is available for evaluation. Also indicate if the product was returned to the manufacturer and, if so, the date of the return.

SECTION D: SUSPECT PRODUCT(S)

For adverse event reporting:

A suspect product is one that you suspect is associated with the adverse event. In **Section F** enter other concomitant medical products (drugs, biologics including human cells, tissues, and cellular and tissue-based products (HCT/Ps), medical devices, etc.) that the patient was using at the time of the event but which you do not think were involved in the event.

Up to two (2) suspect products may be reported on one form (#1=first suspect product, #2=second suspect product). Attach an additional form if there were more than two suspect products associated with the reported adverse event.

For product quality problem reporting:

A suspect product is the product that is the subject of the report. A separate form should be submitted for each individual product problem report.

Identification of the labeler/distributor and pharmaceutical manufacturer and labeled strength of the product is important for prescription or non-prescription products.

This section may also be used to report on special nutritional products (e.g., dietary supplements, infant formula or medical foods), cosmetics, human cells, tissues, or cellular and tissue-based products (HCT/Ps) or other products regulated by FDA.

If reporting on a special nutritional or drug product quality problem, please attach labeling/packaging if available.

If reporting on a special nutritional product only, please provide directions for use as listed on the product labeling.

D1: Name, Strength, Manufacturer

Use the trade/brand name. If the trade/brand name is not known or if there is no trade/brand name, use the generic product name and the name of the manufacturer or labeler. These names are usually found on the product packaging or labeling. Strength is the amount in each tablet or capsule, the concentration of an injectable, etc. (such as "10mg", "100 units/cc", etc.).

For human cells, tissues, and cellular and tissue-based products (HCT/Ps), please provide the common name of the HCT/P. You can also indicate if the HCT/P has a proprietary or trade name. Examples: Achilles tendon, Iliac crest bone or Islet cells.

D2: Dose or Amount, Frequency, Route

Describe how the product was used by the patient (e.g., 500 mg QID orally or 10 mg every other day IV). For reports involving overdoses, the amount of product used in the overdose should be listed, not the prescribed amount. (See **APPENDIX** for list of **Routes of Administration** on the next page.)

D3: Dates of Use

Provide the date administration was started (or best estimate) and the date stopped (or best estimate). If no dates are known, an estimated duration is acceptable (e.g., 2 years) or if therapy was less than one day, then duration is appropriate (e.g., 1 dose or 1 hour for an IV).

For human cells, tissues, and cellular and tissue-based products, provide the date of transplant and if applicable, the date of explanation.

D4: Diagnosis or Reason for Use (Indication)

Provide the reason or indication for which the product was prescribed or used in this particular patient.

D5: Event Abated After Use Stopped or Dose Reduced

If available, this information is particularly useful in the evaluation of a suspected adverse event. In addition to checking the appropriate box, please provide supporting lab tests and dates, if available, in block **B6**.

D6: Lot #

If known, include the lot number(s) with all product quality problem reports, or any adverse event report with a biologic, or medication.

D7: Expiration Date

Please include if available.

(continued on next page)

Appendix D
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SECTION D: SUSPECT PRODUCT(S) *(continued)*

D8: Event Reappeared After Reintroduction

This information is particularly useful in the evaluation of a suspected adverse event. In addition to checking the appropriate box, please provide a description of what happened when the drug was stopped and then restarted in block **B5**, and any supporting lab tests and dates in block **B6**.

D9: NDC # or Unique ID

The national drug code (NDC #) is requested only when reporting a drug product problem. Zeros and dashes should be included as they appear on the label. NDC # can be found on the original product label and/or packaging, but is usually not found on dispensed pharmacy prescriptions.

If the product has a unique or distinct identification code, please provide this here. This is applicable to human cells, tissues, and cellular and tissue-based products (HCT/Ps).

Appendix - Routes of Administration

Auricular (otic) 001
Buccal 002
Cutaneous 003
Dental 004
Endocervical 005
Endosinusial 006
Endotracheal 007
Epidural 008
Extra-amniotic 009
Hemodialysis 010
Intra corpus cavernosum 011
Intra-amniotic 012
Intra-arterial 013
Intra-articular 014
Intra-uterine 015
Intracardiac 016
Intracavernous 017
Intracerebral 018
Intracervical 019
Intracisternal 020
Intracorneal 021
Intracoronary 022
Intradermal 023
Intradiscal (intraspinal) 024
Intrahepatic 025
Intralesional 026
Intralymphatic 027
Intramedullar (bone marrow) 028
Intrameningeal 029
Intramuscular 030
Intraocular 031
Intrapericardial 032
Intraperitoneal 033
Intrapleural 034
Intrasynovial 035
Intratumor 036
Intrathecal 037
Intrathoracic 038
Intratracheal 039
Intravenous bolus 040
Intravenous drip 041
Intravenous (not otherwise specified) 042
Intravesical 043
Iontophoresis 044
Occlusive dressing technique 045
Ophthalmic 046
Oral 047
Oropharingeal 048
Other 049
Parenteral 050
Periarticular 051
Perineural 052
Rectal 053
Respiratory (inhalation) 054
Retrobulbar 055
Subconjunctival 056
Subcutaneous 057
Subdermal 058
Sublingual 059
Topical 060
Transdermal 061
Transmammary 062
Transplacental 063
Unknown 064
Urethral 065
Vaginal 066

Appendix D
MedWatch Form FDA 3500 (cont'd)

SECTION E: SUSPECT MEDICAL DEVICE

The suspect medical device is 1) the device that may have caused or contributed to the adverse event or 2) the device that malfunctioned.

In **Section F**, report other concomitant medical products (drugs, biologics including HCT/Ps, medical devices, etc.) that the patient was using at the time of the event but which you do not think were involved in the event.

If more than one suspect medical device was involved in the event, complete all of **Section E** for the first device and attach a separate completed **Section E** for each additional device.

If the suspect medical device is a single-use device that has been reprocessed, then the reprocessor is now the device manufacturer.

E1: Brand Name

The trade or proprietary name of the suspect medical device as used in product labeling or in the catalog (e.g., Flo-Easy Catheter, Reliable Heart Pacemaker, etc.). This information may 1) be on a label attached to a durable device, 2) be on a package of a disposable device, or 3) appear in labeling materials of an implantable device. Reprocessed single-use devices may bear the Original Equipment Manufacturer (OEM) brand name. If the suspect device is a reprocessed single-use device, enter "NA".

E2: Common Device Name

The generic or common name of the suspect medical device or a generally descriptive name (e.g., urological catheter, heart pacemaker, patient restraint, etc.). Please do not use broad generic terms such as "catheter", "valve", "screw", etc.

E3: Manufacturer Name, City and State

If available, list the full name, city and state of the manufacturer of the suspected medical device. If the answer of block **E8** is "yes", then enter the name, city and state of the reprocessor.

E4: Model #, Catalog #, Serial #, Lot #, Expiration Date, Other #

If available, provide any or all identification numbers associated with the suspect medical device exactly as they appear on the device or device labeling. This includes spaces, hyphens, etc.

Model #:

The exact model number found on the device label or accompanying packaging.

Catalog #:

The exact number as it appears in the manufacturer's catalog, device labeling, or accompanying packaging.

Serial #:

This number can be found on the device label or accompanying packaging; it is assigned by the manufacturer, and should be specific to each device.

Lot #:

This number can be found on the label or packaging material.

Expiration Date (mm/dd/yyyy):

If available, this date can often be found on the device itself or printed on the accompanying packaging.

Other #:

Any other applicable identification number (e.g., component number, product number, part bar-coded product ID, etc.)

E5: Operator of Device

Indicate the type (not the name) of person operating or using the suspect medical device on the patient at the time of the event as follows:

- Health professional = physician, nurse, respiratory therapist, etc.
- Lay user/patient = person being treated, parent/spouse/friend of the patient
- Other = nurses aide, orderly, etc.

E6: If Implanted, Give Gate (mm/dd/yyyy)

For medical devices that are implanted in the patient, provide the implant date or your best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable.

E7: If Explanted, Give Date (mm/dd/yyyy)

If an implanted device was removed from the patient, provide the explantation date or your best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable.

E8: Is this a Single-use Device that was returned before Reprocessed and Reused on a Patient?

Indicate "Yes" or "No".

E9: If Yes to Item No. 8, Enter Name and Address of Reprocessor

Enter the name and address of the reprocessor of the single-use device. Anyone who reprocesses single-use devices for reuse in humans is the manufacturer of the reprocessed device.

Appendix D
MedWatch Form FDA 3500 (cont'd)

SECTION F: OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)
Information on the use of concomitant medical products can frequently provide insight into previously unknown interactions between products, or provide an alternative explanation for the observed adverse event. Please list and provide product names and therapy dates for any other medical products (drugs, biologics including HCT/Ps, medical devices, etc.) that the patient was using at the time of the event. Do not include products used to treat the event.

SECTION G: REPORTER

FDA recognizes that confidentiality is an important concern in the context of adverse event reporting. The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. However, to allow for timely follow-up in serious cases, the reporter's identity may be shared with the manufacturer unless specifically requested otherwise in block G5. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

G1: Name, Address, Phone #, E-mail

Please provide the name, mailing address, phone number and E-mail address of the person who can be contacted to provide information on the event if follow-up is necessary. While optional, providing the fax number would be most helpful, if available. This person will also receive an acknowledgment letter from FDA on receipt of the report.

G2: Health Professional?

Please indicate whether you are a health professional (e.g., physician, pharmacist, nurse, etc.) or not.

G3: Occupation:

Please indicate your occupation (particularly type of health professional), and include specialty, if appropriate.

G4: Also Reported to:

Please indicate whether you have also notified or submitted a copy of this report to the manufacturer and/or distributor of the product, or, in the case of medical device reports only, to the user facility (institution) in which the event occurred. This information helps to track duplicate reports in the FDA database.

G5: Release of reporter's Identity to the manufacturer

In the case of a serious adverse event, FDA may provide name, address and phone number of the reporter denoted in block **G1** to the manufacturer of the suspect product. If you do not want your identity released to the manufacturer, please put an X in this box.