Phase II Randomized Trial of Onartuzumab (MetMAb) in Combination with Erlotinib in Patients with Advanced Non-Small-Cell Lung Cancer

Spigel, et al

DOI: 10.1200/JCO.2012.47.4189

PROTOCOL

TITLE:	**A RANDOMIZED, PHASE II, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND ACTIVITY OF MetMAb, A MONOVALENT ANTAGONIST ANTIBODY TO THE RECEPTOR MET, ADMINISTERED TO PATIENTS WITH ADVANCED NON–SMALL CELL LUNG CANCER, IN COMBINATION WITH TARCEVA® (ERLOTINIB)**
PROTOCOL NUMBER:	OAM4558g
EUDRACT NUMBER:	2008-006939-13
STUDY DRUG:	MetMAb
IND:	100,537
MEDICAL MONITOR:	*Premal H. Patel, M.D., Ph.D.* Phone: +1-650-*225-6791*
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	22 January 2009
DATE AMENDED:	24 February 2010

TABLE OF CONTENTS

Page

TABLE OF CONTENTS(cont'd)

Page

TABLE OF CONTENTS(cont'd)

Page

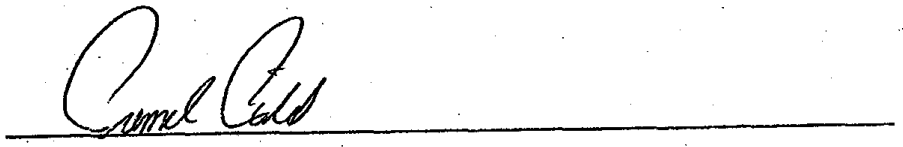
TABLE OF CONTENTS(cont'd)

Page

PROTOCOL AMENDMENT FINALIZATION SIGNATURE PAGE

TITLE:	**A RANDOMIZED, PHASE II, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND ACTIVITY OF MetMAb, A MONOVALENT ANTAGONIST ANTIBODY TO THE RECEPTOR MET, ADMINISTERED TO PATIENTS WITH ADVANCED NON–SMALL CELL LUNG CANCER, IN COMBINATION WITH TARCEVA® (ERLOTINIB)**
PROTOCOL NUMBER:	OAM4558g
EUDRACT NUMBER:	2008-006939-13
STUDY DRUG:	MetMAb
IND:	100,537
MEDICAL MONITOR:	Premal H. Patel, M.D., Ph.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	24 February 2010

This protocol was amended on the date shown above.



Premal H. Patel, M.D., Ph.D.

2/24/10

Date

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, PHASE II, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND ACTIVITY OF MetMAb, A MONOVALENT ANTAGONIST ANTIBODY TO THE RECEPTOR MET, ADMINISTERED TO PATIENTS WITH ADVANCED NON–SMALL CELL LUNG CANCER, IN COMBINATION WITH TARCEVA® (ERLOTINIB)**
PROTOCOL NUMBER:	OAM4558g
EUDRACT NUMBER:	2008-006939-13
STUDY DRUG:	MetMAb
IND:	100,537
MEDICAL MONITOR:	*Premal H. Patel, M.D., Ph.D.*
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	22 January 2009
DATE AMENDED:	24 February 2010

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

_____

Principal Investigator Name (print)

_____ _____

Principal Investigator Signature Date

Please return a copy of the form to a PAREXEL representative. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, PHASE II, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND ACTIVITY OF MetMAb, A MONOVALENT ANTAGONIST ANTIBODY TO THE RECEPTOR MET, ADMINISTERED TO PATIENTS WITH ADVANCED NON–SMALL CELL LUNG CANCER, IN COMBINATION WITH TARCEVA® (ERLOTINIB)**
PROTOCOL NUMBER:	OAM4558g
EUDRACT NUMBER:	2008-006939-13
STUDY DRUG:	MetMAb
PHASE:	II
INDICATION:	NSCLC
IND:	100,537
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	22 January 2009
DATE AMENDED:	24 February 2010

OBJECTIVES

Primary Objective

The primary objective of this study is to evaluate progression-free survival (PFS) of MetMAb + erlotinib, relative to erlotinib + placebo, in patients with Met positive tumors (as determined by immunohistochemistry), as well as *in the "*overall*" patient population*.

Secondary Objectives

The secondary objectives of this study are:

- *To evaluate PFS in patients with squamous cell histology*
- To determine the overall RECIST *1.0* response rate and duration of response in patients with Met positive tumors*, squamous cell histology,* as well as *in the "overall" patient population*
- To characterize the safety and tolerability of MetMAb + erlotinib in patients with *non–small cell lung cancer* (NSCLC)
- To evaluate minimum concentration (C_{min}) and maximum concentration (C_{max}) of both MetMAb and erlotinib in patients with NSCLC

Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate overall survival, in patients with *squamous cell histology,* Met positive tumors, as well as *in the "overall" population*
- To evaluate the FDG-PET response rate, by treatment group and in Met positive tumors, *squamous cell histology,* as well as *in the "overall" population*
- To evaluate PFS in FDG-PET responders versus non-responders, *by* treatment group and in Met positive tumors, *squamous cell histology,* as well as *in the "overall" population*
- To evaluate the relationship between RECIST *1.0* response at first tumor assessment and PFS
- To evaluate the relationship between response and changes in biomarkers (or baseline expression of) related to the HGF/Met and/or EGFR signaling pathways (including, but not limited to IL8 and serum HGF)
- To evaluate potential mechanisms of resistance in patients who progress on study

STUDY DESIGN

This is a Phase II, double-blind, randomized, multicenter trial designed to evaluate the preliminary activity and safety of treatment with MetMAb + erlotinib versus erlotinib + placebo in second- and third-line NSCLC. *Approximately* 120 *histologically unspecified* patients *("overall" population), followed by approximately 50 patients with squamous cell histology* from approximately *40* multinational sites will be randomized in a 1:1 ratio to one of the two treatment arms: MetMAb + erlotinib versus erlotinib + placebo. *Once 120 patients, comprising the "overall" population have enrolled, eligibility will be restricted to patients with squamous cell carcinoma (SCC) histology to ensure that a total of approximately 80 patients with SCC are enrolled in the study*. Randomization *for the first 120 patients comprising the "overall" population* will be stratified by smoking status, performance status, and histology, *and randomization for the next 50 SCC patients will be stratified by smoking status and performance status*. During this study, patients and treating individuals, including the investigators, will be blinded to the treatment assignment of study drug (MetMAb or placebo). Select Genentech staff (i.e., the Safety Review Team) will be unblinded to the treatment assignment. Treatment in each arm will be continued until progression of disease, unacceptable toxicity, or any other discontinuation criterion is met. Upon disease progression, patients randomized to the erlotinib + placebo arm will be given the option to receive MetMAb (in addition to continuing erlotinib), provided they continue to meet eligibility criteria. Safety data collected from this cross-over will be summarized for hypothesis-generating purposes.

During the study, data on tumor measurement and survival status will be collected for evaluation of PFS, overall survival, and overall response rate (ORR). CT scans will be obtained at baseline and for the first four cycles approximately every 6 weeks (every two cycles of MetMAb/placebo). After four cycles, routine CT scans will be performed approximately every 9 weeks (every three cycles of MetMAb/placebo). FDG-PET imaging will be obtained at baseline and at Day 14 (Day 10–14) of Cycle 1. *Throughout the course* of this study, *an* Image Reading Facility (IRF) will evaluate FDG-PET results *and together with the Sponsor* will determine whether FDG-PET *imaging* should *continue* in all *participating sites or whether FDG-PET imaging should be confined to a few sites based on the quality of the data received.*

To support the primary endpoint, all enrolled patients must consent to provide tissue for diagnostic analysis. Met-positive tumors will be identified by an IHC immunohistochemistry (IHC) test which was developed on the basis of internal data from tissue microarrays containing NSCLC specimens. In the absence of archival tissue, fresh *core or excisional* tissue biopsy samples, excluding *fine-needle aspiration and cylology* specimens, will be acceptable.

To characterize the safety/tolerability profile of the combination of MetMAb and erlotinib, patients will be monitored throughout the study for adverse events, changes in laboratory values, and physical examination findings. No overlapping significant toxicities between MetMAb and erlotinib are expected; however, in the absence of a formal safety study, the first 12 patients enrolled in the study will be required to undergo more frequent monitoring. An unblinded Safety Review Team (consisting of at least the Genentech Medical Monitor, the biostatistician, and a drug safety officer) will review safety data from these first 12 patients. Any outcome of this early safety review will be communicated in a timely manner to the investigators for notification of the IRBs/ECs.

Additionally, PK samples will be collected during the study to evaluate minimum concentration (C_{min}) and maximum concentration (C_{max}) of both MetMAb and erlotinib.

Exploratory serum and plasma samples will be collected (optional) to determine the effect of MetMAb + erlotinib on circulating levels of potential markers of activity, including but not limited to IL-8 and HGF. In the Phase I dose-escalation study with MetMAb, drug treatment appears to result in a reduction in circulating levels of IL-8 within 24 hours of the first dose in patients with IL-8 levels above normal. In the same study, most patients showed non-significant increases in circulating serum HGF with drug treatment. Correlating these and other markers with clinical outcomes may assist in identifying predictive biomarkers. Blood for serum and plasma will be drawn from consenting patients at pre-specified times and will be evaluated for levels of these exploratory markers.

OUTCOME MEASURES

Primary Outcome Measure

The primary outcome measure of this study is PFS defined as the time from randomization to the first occurrence of progression or relapse (defined by the Response Evaluation Criteria In Solid Tumors (RECIST *1.0*) and as assessed by the site radiologist and/or site investigator) or death from any cause within 30 days of the last treatment.

Secondary Outcome Measures

The secondary outcome measures for this study are as follows:

- OR (partial response + complete response) as determined using RECIST *1.0*
- Duration of OR, defined as the period from the date of initial, partial, or complete response (as determined using RECIST *1.0*) until date of progression (using RECIST *1.0*) or death from any cause on within 30 days of the last study treatment

Primary and secondary outcome measures will be assessed in patients with MET-positive tumors, in SCC *patients, and in the "overall" patient population.*

SAFETY PLAN

There are no overlapping, significant toxicities between MetMAb and erlotinib, and no drug-drug interactions are expected to occur between a small molecule and an antibody. However, since MetMAb + erlotinib has never been previously studied for safety, an unblinded Safety Review Team will perform a thorough review of safety for the first 12 patients enrolled. These patients will undergo more-frequent monitoring during the first two cycles of treatment. Accrual will not be halted while the analysis is being conducted. If safety signals arise from this review, Genentech may recommend discontinuation of enrollment or a change to the study protocol. All enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and any adverse events requiring study drug interruption or discontinuation. Patients who, at time of progression, have an ongoing adverse event leading to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow up, or the patient starts a different anti-tumor therapy.

Specific safety monitoring procedures for erlotinib include the following:

- Skin toxicities will be monitored by routine physical examination.
- Diarrhea will be monitored by routine symptom history.
- Symptoms consistent with interstitial lung disease—such as new-onset dyspnea, cough, or fever without an obvious cause—should be evaluated. In the event that interstitial lung disease is suspected, erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often administered. Erlotinib should not be restarted in patients suspected of having drug-related interstitial lung disease.
- Erlotinib has rarely been associated with hepatic and/or renal failure in patients with pre-existing hepatic impairment. Patients will be monitored for any possible hepatotoxicity or renal impairment with periodic laboratory assessments, which include certain liver-function tests and serum creatinine levels (see Section 4.5.1d). Patients with significant pre-existing hepatic disease will be not be eligible to participate in this study (see inclusion/exclusion criteria).

Because of the potential for drug–drug interaction between erlotinib and warfarin, patients who are receiving concomitant prophylactic or low-dose warfarin therapy or its equivalent (i.e., unfractionated and/or low-molecular-weight heparin) should be monitored closely for bleeding or changes in International Normalized Ratio (INR).

Toxicity due to erlotinib administration may be managed by symptomatic treatment, dose interruptions (dose interruptions should not exceed more than approximately 7 consecutive days) and/or adjustments of the erlotinib dose. Dose escalations are not allowed following a dose reduction.

Any toxicities associated or possibly associated with MetMAb/placebo administration should be managed according to standard medical practice.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

STUDY TREATMENT

Trial Drug

a. Formulation

MetMAb will be supplied as a sterile liquid in a single-use 15-cc vial. Each vial contains 600 mg of MetMAb in 10 mL at a concentration of 60 mg/mL in 10 mM histidine acetate, 120mM trehalose, 0.02% polysorbate 20, pH 5.4.

Placebo will consist of 250 cc 0.9% NSS (Saline IV solution, 0.9%) and will be provided by the investigative site.

Erlotinib oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. In addition to the active ingredient (erlotinib), tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and magnesium stearate.

Tablets containing 25 mg, 100 mg, and 150 mg of erlotinib are available.

b. Dosage, Administration, and Storage

MetMAb will be administered as an IV infusion. The total dose of MetMAb for each patient will be 15mg/kg in 250 cc final 0.9% NSS. The weight at screening will be used to determine the actual dose of MetMAb. This dose will be administered throughout the study and will not change according to weight.

Active study drug will be administered intravenously, after dilution in normal saline (0.9%). The volume of MetMAb to be given will be calculated for each patient. A volume of sterile saline equal to the calculated volume of MetMAb from the vial will be withdrawn from the normal saline IV bag and discarded. The calculated volume of study drug will be drawn into a syringe and injected into the normal saline IV bag. Mix the IV bag by gently inverting after injecting the study drug, do not shake. Once MetMAb has been diluted, it must be used within 8 hours. *If diluted MetMAb needs to be transported to another facility, it should be diluted in PVC bags and transported at 5°C.*

The 250-cc final volume of 0.9% NSS containing MetMAb/placebo infusion will be administered over 60 (± 10) minutes as a continuous IV infusion on Day 1 of the first four cycles. Patients will be observed for approximately 60 minutes after completion of the infusion for fever, chills, or other infusion-associated symptoms. After the first four cycles, the MetMAb/placebo infusion may be delivered over 30 (±10) minutes, provided the patient tolerated the previous 4 infusions.

Upon receipt, vials containing MetMAb must be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. Vials used for one patient may not be used for any other patient. VIALS ARE FOR SINGLE USE ONLY. Any remaining solution should be discarded. Dextrose should not be used for dilution of MetMAb.

The dose of erlotinib will be 150 mg by mouth (PO) daily (QD). Dosing of erlotinib on the days of the MetMAb/placebo infusion will be done in the clinic. This dose may be reduced as outlined in under “Dosage Modification” below. Tablets should be taken preferably in the morning with approximately 200 mL water, at least 1 hour before or 2 hours after a meal.

Patient compliance in taking the assigned erlotinib daily dose will be assessed by standard pill counts. Bottles and blister packages containing erlotinib tablets will be given to patients at regularly scheduled visits. Previously distributed bottles and blister packages will be returned to the clinic and counted; discrepancies will be resolved with the patient at each clinic visit and documented in the patient’s medical chart.

Erlotinib has only been studied in patients over the age of 18 years. Current data do not show a need for a different initial dose in elderly populations.

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

Infusion Modification

The MetMAb/placebo infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. If infusion-related symptoms occur, patients will be treated according to best medical practice and will be monitored until adequate resolution of signs and symptoms. Study treatment will be administered in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. Patients who experience MetMAb/placebo infusion–associated symptoms may be pre-medicated appropriately (e.g., with NSAIDS, acetaminophen and/or diphenhydramine for subsequent infusions). The use of any steroids requires *prior* approval by the Medical Monitor. Please refer to Section 5 for additional information regarding the management of adverse events related to MetMAb.

Infusion Schedule Modification

If a treatment interruption is required, MetMAb/placebo dosing may be delayed by up to 7 days (dose delays longer than 7 days may be considered pending discussion with the Medical Monitor). If a patient has required two dose delays for the same adverse event and within the first four cycles, the patient may continue dosing on a 28-day cycle, pending discussion with the Medical Monitor. If a scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date and subsequent dosing should continue on a 21-day schedule.

Dosage Modification

No modification of the MetMAb/placebo dose will be allowed during this study.

Dose reduction or interruption of erlotinib for toxicity likely attributable to erlotinib (e.g., rash, diarrhea) may take place at any time during the study. Dose interruptions should not exceed more than approximately 7 consecutive days. Dose level reductions are presented in Table 1. If a patient does not tolerate erlotinib at 50 mg, then *erlotinib* treatment should be discontinued*; the patient may continue on MetMAb/placebo, at the discretion of the investigator, following consultation with* the Medical Monitor. *Patients may continue on single-agent MetMAb (as randomized) if discontinuation of erlotinib is required because of tolerability issues, upon discussion with the Medical Monitor.*

Management of Toxicities Related to Study Treatment

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

CONCOMITANT THERAPY AND CLINICAL PRACTICE

All concomitant treatments (medications or procedures) within the 14 days preceding the initial study drug infusion on this study through Cycle 4 will be recorded; after that, any new concomitant treatments and any changes to the daily dosing will be recorded as part of the targeted history/physical examination. The reason(s) for treatment, dosage, and dates of treatment will be reported to the investigator and recorded as instructed on the study-specific case report form (CRFs).

- Patients should receive full supportive care, including hematopoietic growth factors, transfusions of blood and blood products, antibiotics, etc., when appropriate
- Appropriate prophylactic anti-emetic regimens should be provided to all patients who develop ≥ Grade 2 nausea and vomiting
- Patients who experience infusion-associated symptoms may be treated as clinically indicated, including ≤ 48 hours of treatment with corticosteroids. Pre-medication other than acetaminophen, NSAIDS, or diphenhydramine must be discussed with the Medical Monitor.

  If use of steroids is required, it is recommended that the dosing remains stable between the time of the two FDG-PET scans because steroid use may result in increased blood glucose levels, which would affect FDG uptake and potentially lead to a false assessment of PET response.
- 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 erlotinib and warfarin, it is preferable that patients not use warfarin for this purpose.
- Other medication considered necessary for the patient's safety and well-being may be given at the discretion of the investigator(s).

- Because erlotinib is metabolized by the CYP3A4 pathway, agents known to inhibit or induce CYP3A4 function may alter the pharmacokinetics of erlotinib. Although caution and careful monitoring are recommended when use of these compounds is necessary, usage does not exclude patient participation in this trial.
- Use of systemic corticosteroids for the treatment of skin toxicities is discouraged.

STATISTICAL METHODS

Primary Efficacy Analysis

Kaplan–Meier methodology will be used to estimate the median PFS for each treatment arm. The stratification factors will be determined by the CRF data, not by data collected by the IVRS at the time of randomization unless the CRF data is missing. Estimation of the hazard ratio (i.e., the magnitude of treatment effect and 95% confidence interval) will be determined using a stratified Cox regression model with an indicator variable for MetMAb treatment.

The same analysis methods as those described for PFS in *"overall" population* patients are applied to *patients with Met* positive *tumors and to patients with SCC histology*. All deaths from any cause within 30 days of the last treatment will be included as PFS events.

Missing Data

For PFS, data for patients who are lost to follow-up will be treated as censored on the last date the patient was known to be progression free. Data for patients who are randomized and not treated and who do not have any post-randomization tumor assessments will be treated as censored on the randomization day plus 1 day.

For survival, data for patients who are lost to follow-up will be treated as censored on the last date the patient was known to be alive. This may be the randomization date plus 1 day for patients who are randomized, not treated, and immediately lost to follow-up.

For objective response, patients without a post-baseline tumor assessment will be counted as a non-responder.

Determination of Sample Size

This Phase II trial is designed to make a preliminary assessment of the safety and activity of MetMAb + erlotinib in patients with NSCLC who have relapsed following one or two prior regimens; special attention is given to outcomes in patients with Met positive tumors *and patients with squamous cell histology*. The study will *initially* accrue *approximately*120 *histologically unspecified ("overall" population)* patients; it is expected that about 50% of the enrolled patients (30 per arm) *will* have Met positive tumors by IHC. *For evaluation of the primary endpoint, p*atients will be followed *until the time of* approximately 42 investigator-assessed PFS events among patients with Met positive tumors *in the "overall" population. In addition, this study will accrue approximately 80 total SCC patients (approximately 30 in the "overall" population, followed by accrual of approximately 50 subsequent SCC patients). A PFS analysis among patients with squamous histology will occur when approximately 55 investigator-assessed PFS events have been observed.*

This Phase II trial is hypothesis-generating and is able to detect only a large benefit of combination therapy with MetMAb + erlotinib. For example, with 42 events in patients with Met-positive tumors, there is 80% power to detect, at a one-sided significance level of 0.025, an HR of 0.4 in MetMAb + erlotinib, compared with erlotinib + placebo. This trial however, will not have adequate power to detect minimum clinically meaningful differences between the treatment arms. For example, there is only 21% of power to detect an HR of 0.7. Thus, formal hypothesis testing is limited in that statistically negative outcomes do not necessarily rule out clinically significant treatment effects.

1. BACKGROUND

Hepatocyte growth factor (HGF) and its receptor, the tyrosine kinase Met, promote cell proliferation, motility, invasion, and survival, as well as dramatic morphogenic changes that in turn stimulate tissue repair and regeneration and tumor growth (Stoker et al. 1987; Miyazawa 1989; Nakamura et al. 1989; Zarnegar et al. 1989; Gherardi et al. 1990; Bottaro et al. 1991; Weidner et al. 1991; Ma et al. 2003).

The HGF/Met pathway is frequently dysregulated in many human malignancies. Met over-expression, with or without gene amplification, has been reported in a variety of human tumor types, including, but not limited to, colorectal, breast, lung, and gastric cancers and hepatocellular carcinomas (Kuniyasu et al. 1993; Boix et al. 1994). Moreover, activating genetic alterations of Met have been documented in papillary renal cell carcinomas (Schmidt and Danilkovitch-Miagkova 2002). High levels of HGF and/or Met have also been correlated with poor prognosis in several tumor types, including non–small cell lung cancer (NSCLC), breast cancer, ovarian cancer, cervical cancer, gastric cancer, transitional bladder carcinoma, glioblastoma, head and neck cancers, and multiple myeloma (Ichimura et al. 1996; Koochekpour et al. 1997; Wu et al. 1998; Turesson et al. 1999; Uchida et al. 2001; Baykal et al. 2003; Masuya et al. 2004; Ayhan et al. 2005; Cheng et al. 2005; Lengyal et al. 2005). Finally, activation of Met has been implicated in angiogenesis in vivo, most likely through an indirect means of upregulating expression of angiogenic factors, such as vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8). Collectively, these findings provide a compelling link between activation of the Met pathway and malignancy.

1.1 BACKGROUND ON DISEASE

Lung cancer remains one of the leading causes of cancer death worldwide; it is the second most common cancer in both men and women and accounts for approximately 15% of all new cancers. In 2008, it is estimated that there will be approximately 215,000 new cases of lung cancer and an estimated 160,000 deaths in the United States. Only about 15% of people diagnosed with lung cancer remain alive after 5 years. NSCLC is one of the two major types of lung cancer, accounting for approximately 85% of all lung cancer cases.

Many chemotherapies have activity in Stage IIIb/IV NSCLC, especially when given in combination. Targeted agents, such as Tarceva® (erlotinib) have also been found to have activity. Erlotinib inhibits the Epidermal Growth Factor Receptor (EGFR) protein and was shown to prolong survival, when administered as a single agent in the second or third line, to unselected patients with NSCLC (Shepherd et al. 2004). Tarceva was approved in the United States in 2004 and in Europe in 2005 for the treatment of patients with locally advanced or metastatic NSCLC following failure of at least one prior chemotherapy regimen.

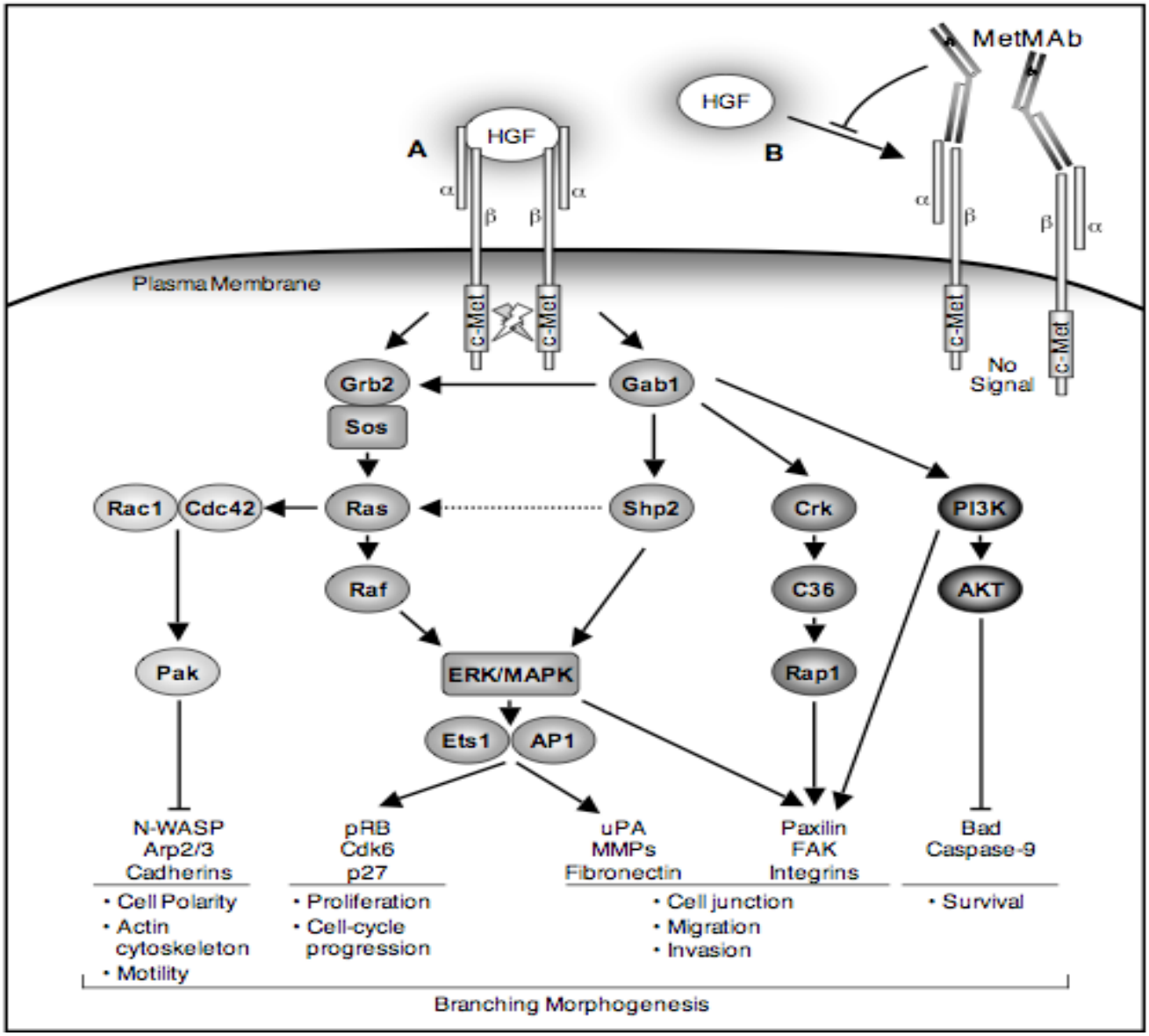
There is growing evidence that the two major NSCLC histologic subtypes, adenocarcinoma (accounting for ~40% of lung cancer) and squamous cell carcinoma (SCC; accounting for ~25% of lung cancer) exhibit unique biologic properties, resulting in differential responses to similar therapies. Pemetrexed, while active in adenocarcinoma, has shown relatively lower efficacy in SCC (Scagliotti et al. 2008). Treatment with bevacizumab in NSCLC patients with centrally located SCC has resulted in increased bleeding risk (Sandler et al. 2006). Finally, SCC patients with metastatic disease historically have worse overall survival compared with adenocarcinoma, thus an unmet need to identify effective regimens for this histologic subset remains.

1.2 BACKGROUND ON THE MOLECULE

MetMAb is a recombinant, humanized, monovalent monoclonal antibody directed against Met. By binding to the extracellular domain of Met, MetMAb selectively blocks ligand binding and subsequent activation by HGF (Figure 1). The unique monovalent design of MetMAb eliminates the potential for Met activation via receptor dimerization, thought to occur with a bivalent antibody (Prat 1998). MetMAb is the only monovalent antibody—and currently represents the only antibody-based approach in the clinic—that targets the receptor.

Figure 1

Pathways Activated by c-Met following Activation by HGF



HGF = hepatocyte growth factor.

Notes: A) Some of the pathways activated by Met following activation by HGF: downstream of each canonical pathway is a list of the functional cellular response associated with the pathway depicted. Activation of all of the pathways is required for branching morphogenesis to occur. B) MetMAb blocks activation of Met by blocking HGF binding to the receptor, resulting in no signal being generated. This figure is adapted from Birchmeier et al. 2003.

1.3 CLINICAL EXPERIENCE WITH METMAB

MetMAb is being evaluated in a Phase I, open label, dose-escalation clinical trial (OAM4224g) in patients with advanced solid malignancies. In this study, patients receive MetMAb (IV, Q3 weeks) at doses ranging from 1 mg/kg to 30 mg/kg until disease progression. A single dose-limiting toxicity (DLT) of Grade 3 pyrexia occurred at 4 mg/kg. No other DLTs have been observed up to the maximum administered dose of 30 mg/kg. The most commonly reported adverse event was fatigue (Grades 1 and 2).

The recommended Phase II dose of 15 mg/kg administered intravenously every 3 weeks was calculated on the basis of nonclinical pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations based on PK data collected in the Phase I study. This dose is expected to maintain the desired minimum tumoristatic concentration of 15 μg/mL in ≥ 90% of the patients.

1.4 CLINICAL EXPERIENCE WITH ERLOTINIB

Erlotinib has been studied in at least 4900 patients in a number of Phase I, II, and III clinical trials. Please refer to the Tarceva Package Insert for descriptions of all completed Phase I, II, and III trials.

1.4.1 Phase II/III Safety Results

Multiple Phase II and III trials of erlotinib have been conducted in patients with advanced, refractory malignancies. In the Phase III, randomized, placebo-controlled trials, adverse events experienced by patients in the erlotinib arm were generally similar in incidence and severity to those experienced by patients in the placebo arm, with the exception of an increased incidence of rash events and diarrhea.

1.5 RATIONALE FOR DOING THIS STUDY

The EGFR signaling network has been implicated in the growth and development of many human epithelial tumors. As such, multiple EGFR inhibitors have become therapeutic tools for the treatment of human cancers. Unfortunately, in almost every patient who responds to EGFR inhibitors, resistance eventually occurs. Understanding the underlying causes of therapeutic resistance to EGFR inhibitors has therefore been the focus of intensive research. Recently, genetic amplification

and over-expression of Met have been implicated in driving resistance to EGFR inhibitors, both in NSCLC cell lines and in patients (Engelman et al. 2007). Inhibition of either Met or EGFR was insufficient to fully block signaling in gefitinib-resistant cell lines, whereas the combination did inhibit signaling. Other studies have further confirmed the link between resistance to EGFR inhibitors and over-expression and/or amplification of Met in NSCLC (Bean and Zucali et al. 2008). EGFR and Met may cooperate in driving tumorigenesis prior to exposure or acquisition of resistance to EGFR inhibitors (AACR 2008). Met is expressed in approximately 50% of NSCLC (Zucali et al. 2008), and EGFR is expressed in approximately 45%–65% of NSCLC and can be as high as 85% in squamous cell histology (Shepherd et al. 2004; Patel 2006.). Met and EGFR are commonly co-expressed in NSCLC cell lines and human tumors, particularly in adenocarcinomas, where roughly 70% of EGFR-positive tumors also co-express Met (unpublished data). *In this same sample set, and only in the squamous histology subset, Met expression occurred only in tissues with EGFR expression; however, not all SCC tissues with EGFR expression were found to have Met expression, suggesting Met expression may be temporally linked to EGFR expression, at least in this histologic subset (unpublished data).* Furthermore, signaling through Met or EGFR reinforces activation of the other pathway. Activation of EGFR has been shown to induce Met pathway activity (Fisher et al. 2004; Bonine-Summers et al. 2007), and activation of Met has likewise been found to increase the expression of some EGFR ligands (Guo et al. 2008). In support of the cooperative nature of Met and EGFR signaling in untreated tumors, MetMAb demonstrated strong additive effects when combined with erlotinib in the NCI-H596 NSCLC xenograft tumor model (AACR 2008). These data suggest that Met and EGFR cooperate to drive tumor growth and survival and therefore support a strong rationale for combining Met and EGFR inhibitors in the clinic.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate progression-free survival (PFS) of MetMAb + erlotinib, relative to erlotinib + placebo, in patients with Met positive tumors (as determined by immunohistochemistry), as well as *in the "*overall*" patient population*.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- *To evaluate PFS in patients with squamous cell histology*
- To determine the overall RECIST *1.0* response rate and duration of response in patients with Met positive tumors*, squamous cell histology,* as well as *in the "overall" patient population*
- To characterize the safety and tolerability of MetMAb + erlotinib in patients with *non–small cell lung cancer (*NSCLC*)*
- To evaluate minimum concentration (C_{min}) and maximum concentration (C_{max}) of both MetMAb and erlotinib in patients with NSCLC

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are:

- To evaluate overall survival*,* in patients with *squamous cell histology,* Met positive tumors, as well as *in the "overall" population*
- To evaluate the FDG-PET response rate, by treatment group and in Met positive tumors*, squamous cell histology,* as well as *in the "overall" population*
- To evaluate PFS in FDG-PET responders versus non-responders, *by* treatment group and in Met positive tumors*, squamous cell histology,* as well as *in the "overall" population*
- To evaluate the relationship between RECIST *1.0* response at first tumor assessment and PFS
- To evaluate the relationship between response and changes in biomarkers (or baseline expression of) related to the HGF/Met and/or EGFR signaling pathways (including, but not limited to IL8 and serum HGF)
- To evaluate potential mechanisms of resistance in patients who progress on study

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, double-blind, randomized, multicenter trial designed to evaluate the preliminary activity and safety of treatment with MetMAb + erlotinib versus erlotinib + placebo in second- and third-line NSCLC. *Approximately* 120 *histologically unspecified* patients *("overall" population), followed by approximately 50 patients with squamous cell histology* from approximately *40* multinational sites will be randomized

in a 1:1 ratio to one of the two treatment arms: MetMAb + erlotinib versus erlotinib + placebo. *Once 120 patients, comprising the "overall" population have enrolled, eligibility will be restricted to patients with squamous cell carcinoma (SCC) histology to ensure that a total of approximately 80 patients with SCC are enrolled in the study.* Randomization *for the first 120 patients comprising the "overall" population* will be stratified by smoking status, performance status, and histology*, and randomization for the next 50 SCC patients will be stratified by smoking status and performance status.* During this study, patients and treating individuals, including the investigators, will be blinded to the treatment assignment of study drug (MetMAb or placebo). Select Genentech staff (i.e., the Safety Review Team) will be unblinded to the treatment assignment. Treatment in each arm will be continued until progression of disease, unacceptable toxicity, or any other discontinuation criterion is met. Upon disease progression, patients randomized to the erlotinib + placebo arm will be given the option to receive MetMAb (in addition to continuing erlotinib), provided they continue to meet eligibility criteria. Safety data collected from this cross-over will be summarized for hypothesis-generating purposes.

During the study, data on tumor measurement and survival status will be collected for evaluation of PFS, overall survival, and overall response rate (ORR). CT scans will be obtained at baseline and for the first four cycles approximately every 6 weeks (every two cycles of MetMAb/placebo). After four cycles, routine CT scans will be performed approximately every 9 weeks (every three cycles of MetMAb/placebo). FDG-PET imaging will be obtained at baseline and at Day 14 (Day 10–14) of Cycle 1. *Throughout the course* of this study*, an* Image Reading Facility (IRF) will evaluate FDG-PET results *and together with the Sponsor* will determine whether FDG-PET *imaging* should *continue* in all *participating sites or whether FDG-PET imaging should be confined to a few sites based on the quality of the data received.*

To support the primary endpoint, all enrolled patients must consent to provide tissue for diagnostic analysis. Met-positive tumors will be identified by an IHC immunohistochemistry (IHC) test which was developed on the basis of internal data from tissue microarrays containing NSCLC specimens. In the absence of archival tissue, fresh *core or excisional* tissue biopsy samples, excluding *fine-needle aspiration and cylology* specimens, will be acceptable.

To characterize the safety/tolerability profile of the combination of MetMAb and erlotinib, patients will be monitored throughout the study for adverse events,

changes in laboratory values, and physical examination findings. No overlapping significant toxicities between MetMAb and erlotinib are expected; however, in the absence of a formal safety study, the first 12 patients enrolled in the study will be required to undergo more frequent monitoring. An unblinded Safety Review Team (consisting of at least the Genentech Medical Monitor, the biostatistician, and a drug safety officer) will review safety data from these first 12 patients. Any outcome of this early safety review will be communicated in a timely manner to the investigators for notification of the IRBs/ECs. Additionally, PK samples will be collected during the study to evaluate minimum concentration (C_{min}) and maximum concentration (C_{max}) of both MetMAb and erlotinib.

Exploratory serum and plasma samples will be collected (optional) to determine the effect of MetMAb + erlotinib on circulating levels of potential markers of activity, including but not limited to IL-8 and HGF. In the Phase I dose-escalation study with MetMAb, drug treatment appears to result in a reduction in circulating levels of IL-8 within 24 hours of the first dose in patients with IL-8 levels above normal. In the same study, most patients showed non-significant increases in circulating serum HGF with drug treatment. Correlating these and other markers with clinical outcomes may assist in identifying predictive biomarkers. Blood for serum and plasma will be drawn from consenting patients at pre-specified times and will be evaluated for levels of these exploratory markers.

3.2 RATIONALE FOR STUDY DESIGN

The rationale for the study design is based on the hypothesis that combining MetMAb with erlotinib will prolong PFS compared with erlotinib monotherapy in the setting of second- and third-line therapy for patients with NSCLC, as discussed above.

Along with assessments for the safety and tolerability of MetMAb, in combination with erlotinib, patients will be evaluated for disease progression at predefined, standard intervals to minimize evaluation-time biases.

In this study, tumor samples are required to evaluate for Met expression by IHC. This data will be used to support the hypothesis that Met expression is predictive of response to MetMAb, as well as to inform patient selection for future studies with MetMAb.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measure

The primary outcome measure of this study is PFS defined as the time from randomization to the first occurrence of progression or relapse (defined by the Response Evaluation Criteria In Solid Tumors (RECIST *1.0*) and as assessed by the site radiologist and/or site investigator) or death from any cause within 30 days of the last treatment.

3.3.2 Secondary Outcome Measures

The secondary outcome measures for this study are as follows:

- OR (partial response + complete response) as determined using RECIST *1.0*
- Duration of OR, defined as the period from the date of initial, partial, or complete response (as determined using RECIST *1.0*) until date of progression (using RECIST *1.0*) or death from any cause *within 30 days of the last* study treatment

Primary and secondary outcome measures will be assessed in patients with MET positive tumors, in SCC patients, and in the "overall" patient population.

3.3.3 Safety Outcome Measures

Safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events and serious adverse events
- Changes in vital signs and clinical laboratory results during and following study drug administration
- Assessment of anti-therapeutic antibody (ATA) response to MetMAb

3.3.4 PK/PD Outcome Measures

Serum samples will be collected for analysis of MetMAb, as follows:

- Minimum concentration (C_{min}) will be measured prior to dosing on Day 1 of Cycles 1–4 and every four cycles thereafter (i.e., same time collection as ATA sample) and at study termination
- Maximum concentration (C_{max}) will be measured approximately 1 hour post-infusion on Day 1 of Cycles 1–4
- Every effort should be made to obtain a serum sample at the time of the post-dose FDG-PET scan (±3 hours)

Serum samples to measure ATAs to MetMAb will be collected prior to MetMAb dosing on Day 1 of Cycles 1–4 and every four cycles thereafter (i.e., Cycles 8, 12, etc).

Plasma samples will be collected for analysis of erlotinib, as follows:

- C_{min} will be measured prior to erlotinib dosing on Day 1 of Cycles 1–4 and at study termination
- C_{max} will be measured 2–4 hours post-dose of erlotinib on Day 1 of Cycles 1–4
- Every effort should be made to collect a plasma sample at the time of the post-dose FDG-PET scan (±3 hours)

Since alpha(1)-acid glycoprotein (AAG) is a significant covariate in erlotinib clearance, plasma samples will be collected for AAG measurement prior to dosing on Day 1 of Cycles 1–4.

3.3.5 Exploratory Outcome Measures

Exploratory outcome measures include the following:

- OS, defined as the time from randomization until death from any cause in Met positive tumors and *in the "overall" population*
- FDG-PET response rates, as determined based on the definitions of the European Organization for Research of Cancer (EORTC) and as assessed by an independent, blinded FGD-PET IRF

3.4 SAFETY PLAN

There are no overlapping, significant toxicities between MetMAb and erlotinib, and no drug-drug interactions are expected to occur between a small molecule and an antibody. However, since MetMAb + erlotinib has never been previously studied for safety, an unblinded Safety Review Team will perform a thorough review of safety for the first 12 patients enrolled. These patients will undergo more-frequent monitoring during the first two cycles of treatment. Accrual will not be halted while the analysis is being conducted. If safety signals arise from this review, Genentech may recommend discontinuation of enrollment or a change to the study protocol. All enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and laboratory measurements.

Patients will be evaluated for adverse events (all grades), serious adverse events, and any adverse events requiring study drug interruption or discontinuation. Patients who, at time of progression, have an ongoing adverse event leading to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow up, or the patient starts a different anti-tumor therapy.

Specific safety monitoring procedures for erlotinib include the following:

- Skin toxicities will be monitored by routine physical examination.
- Diarrhea will be monitored by routine symptom history.
- Symptoms consistent with interstitial lung disease—such as new-onset dyspnea, cough, or fever without an obvious cause—should be evaluated. In the event that interstitial lung disease is suspected, erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often administered. Erlotinib should not be restarted in patients suspected of having drug-related interstitial lung disease.
- Erlotinib has rarely been associated with hepatic and/or renal failure in patients with pre-existing hepatic impairment. Patients will be monitored for any possible hepatotoxicity or renal impairment with periodic laboratory assessments, which include certain liver-function tests and serum creatinine levels (see Section 4.5.1d). Patients with significant pre-existing hepatic disease will not be eligible to participate in this study (see inclusion/exclusion criteria).

Because of the potential for drug–drug interaction between erlotinib and warfarin, patients who are receiving concomitant prophylactic or low-dose warfarin therapy or its equivalent (i.e., unfractionated and/or low-molecular-weight heparin) should be monitored closely for bleeding or changes in International Normalized Ratio (INR).

Toxicity due to erlotinib administration may be managed by symptomatic treatment, dose interruptions (dose interruptions should not exceed more than approximately 7 consecutive days) and/or adjustments of the erlotinib dose. Dose escalations are not allowed following a dose reduction.

Any toxicities associated or possibly associated with MetMAb/placebo administration should be managed according to standard medical practice.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

3.5 CONTROL GROUPS

This Phase II trial is a randomized, double-blind, placebo-controlled, multicenter, international trial. The control group enrolled in this study will consist of patients with advanced NSCLC who will be treated with erlotinib + placebo.

3.6 MINIMIZATION OF BIAS

Patients will be randomized in a double-blind fashion to one of two treatment arms by use of an interactive voice response system (IVRS). Randomization *for the first 120 histologically unspecified "overall," population patients* will be stratified by smoking status, performance status, and histology*; and randomization for the next 50 subsequent SCC patients will be stratified by smoking status and performance status*. Patients in both treatment arms will be followed according to the same pre-specified schedule of assessments.

*G*iven the exploratory nature of FDG-PET changes at Day 14 (e.g., FDG-PET flares) it is recommended that no action be taken by the investigators based on FDG-PET findings (exceptions may exist where a new lesion is observed and is deemed to require immediate medical attention, [e.g., a new CNS metastasis]).

3.7 ETHICAL CONSIDERATIONS

The prognosis for patients with NSCLC is poor, with a median survival of approximately 4 months among untreated patients (Bunn and Kelly 1998). For patients who experience disease progression following a platinum-based therapy, median time to disease progression is estimated to be 4.6 weeks without further treatment (Schiller et al. 2002). To date, no therapies have had a major impact in this setting. Single-agent erlotinib is considered a reasonable therapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen; therefore, patients receiving erlotinib + placebo will receive treatment consistent with current standards of care. Erlotinib will be provided by the Sponsor.

3.8 ADMINISTRATIVE STRUCTURE

This trial is sponsored by Genentech. Approximately *40* study centers inside and outside the United States will participate in this study, enrolling a total of approximately *170* patients *(approximately 120 histologically unspecified "overall"*

population patients, followed by approximately 50 additional SCC patients). A Clinical Research Organization (CRO) will provide clinical operations oversight, data management, and medical monitoring. An IVRS will be used to manage site drug supply and to randomize patients to study drug. PK/PD samples will be sent to a central laboratory for sample storage, as specified in Section 4.5. Sample analysis will be performed by an external vendor or Genentech. An IRF will be used to perform blinded central reads of FDG-PET scans.

3.9 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Patient Selection

Adult patients are eligible to participate in this study if they have inoperable locally advanced or metastatic (Stage IIIb/IV) NSCLC and have received at least one, but no more than two prior regimens for Stage IIIb/IV NSCLC disease. In this study, cancer staging will follow the American Joint Committee on Cancer's AJCC Cancer Staging Manual*, sixth edition*. Patients must comply with all eligibility criteria to be enrolled.

4.1.2 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed, written informed consent prior to any study-specific screening procedures
- Age ≥18 years of age
- ECOG performance status of 0, 1, or 2 (see Appendix D)

- Histologically confirmed NSCLC*; following accrual of the first 120 histologically unspecified "overall" population, the subsequent 50 patients must have squamous cell histology*

  Availability at the site of a representative formalin-fixed, paraffin-embedded tumor specimen that enabled the definitive diagnosis of NSCLC with adequate viable tumor cells in a tissue block (preferred) or 15 unstained, serial slides, accompanied by an associated pathology report is required prior to randomization. Cytological *or fine-needle aspiration* samples are not acceptable. If the archival tissue is neither sufficient nor available, the patient may still be eligible, upon discussion with the Medical Monitor, assuming the patient:

  Can provide at least ≥5 unstained, serial slides

  or

  Is willing to consent to and undergo a pre-treatment *core or excisional* biopsy of the tumor. *Cytological or fine-needle aspiration samples are not acceptable.*

- Recurrent or progressive disease following at least one chemo containing regimen for Stage IIIB/IV disease

  Patients who receive neo-adjuvant and/or adjuvant therapy for Stage I–IIIa disease prior to their first-line regimen (for Stage IIIb/IV) are eligible for study participation, provided they also receive first-line therapy for Stage IIIb/IV disease

  At least one of the chemotherapy containing regimens (for any stage) must have been platinum-based

- Measurable disease in accordance with RECIST *1.0* (see Appendix C)

- At least one measurable lesion on a pre-treatment FDG-PET scan that is also a target lesion on CT according to RECIST *1.0* (as determined by the site)

  Throughout the *course* of *this study, an Image Reading Facility (*IRF*)* will *evaluate FDG-PET results and together with the Sponsor will determine* whether *FDG-PET imaging should continue in all participating sites or whether FDG-*PET imaging should be *confined to a few sites based* on *the quality of* the *data received. Therefore*, this criterion may only apply to sites that will continue to perform FDG-PET imaging (see Section 4.5.6).

- Use of an acceptable means of contraception for men and women of childbearing potential

4.1.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- More than two prior treatments for Stage IIIB/IV

  A change of chemotherapy regimen for reasons of patient intolerance or excessive toxicity does not constitute an additional regimen, unless disease progression was documented at the time of treatment change.

  Combined treatment with chemotherapy and radiation constitutes a single prior regimen

  Surgery does not constitute a prior regimen

- More than 30 days of exposure to an investigational or marketed agent that can act by EGFR inhibition, or a known EGFR-related toxicity resulting in dose modifications

  EGFR inhibitors include (but are not limited to) gefitinib, erlotinib, and cetuximab

- Chemotherapy, biologic therapy, radiotherapy or investigational drug within 28 days prior to randomization

  Exceptions are kinase inhibitors, which may be used within 2 weeks prior to randomization, provided that any drug-related toxicity has adequately resolved and prior approval has been obtained from the Medical Monitor

- Untreated and/or active (progressing or requiring anticonvulsants or corticosteroids for symptomatic control) CNS metastasis

  Patients with history of brain metastasis may be eligible for study participation, as long as they meet the following criteria:

  Measurable disease outside the CNS, as defined by RECIST *1.0*

  No radiographic evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Adequate CNS-directed treatment, which may include neurosurgery or stereotactic radiosurgery.

  The screening of CNS radiographic study is ≥4 weeks since completion of radiotherapy and ≥2 weeks since the discontinuation of corticosteroids and anticonvulsants

  Radiotherapy and/or stereotactic radiosurgery must be completed ≥4 weeks prior to Day 1

  Neurosurgery must be completed ≥24 weeks prior to Day 1, and brain biopsy must be completed ≥12 weeks prior to Day 1

- History of serious systemic disease within the past 6 months prior to randomization, including myocardial infarction, uncontrolled hypertension (*persistent* blood pressure > 150/100 mmHg on *antihypertensives*), unstable angina, New York Heart Association (NYHA) Grade II or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication (patients with chronic atrial arrhythmia, i.e., atrial fibrillation or paroxysmal supraventricular tachycardia are eligible), or Grade II or greater peripheral vascular disease
- Uncontrolled diabetes as evidenced by fasting serum glucose level > 200mg/dL
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization
- Anticipation of need for a major surgical procedure during the course of the study
- Local palliative radiotherapy within 7 days prior to randomization or persistent adverse effects from radiotherapy that have not been resolved to Grade II or less prior to randomization
- Inability to take oral medication or requirement for intravenous (IV) alimentation or total parenteral nutrition with lipids, or prior surgical procedures affecting gastrointestinal absorption
- Symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinical significant hypercalcemia are eligible
- Any of the following *uncorrected* abnormal hematologic values (within 2 weeks prior to randomization)

  ANC < 1,500 cells/μL

  Platelet count < 100,000 cells/μL

  Hemoglobin < 9.0 g/dL
- Other baseline laboratory values (within 2 weeks prior to randomization)

  Serum bilirubin > 1.5× ULN

  Alkaline phosphatase, AST and ALT > 2.5 ULN

  Serum creatinine > 1.5×ULN

  Uncontrolled hypercalcemia (> 11.5 mg/dL or > 1.5 ionized calcium)
- Pregnant or breastfeeding women

- Other malignancies that have undergone a putative surgical *or radiotherapy* cure (*specifically,* intraepithelial carcinoma of the cervix uteri, localized prostate cancer post prostatectomy, or basal/squamous cell carcinoma of the skin) within 5 years prior to randomization may be discussed with the Medical Monitor.
- Evidence of confusion or disorientation, or history of major psychiatric illness that may impair the patient's understanding of the Informed Consent Form

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained and eligibility has been established (including tissue availability), the study site will be required to fax the patient's eligibility information to the Medical Monitor prior to randomization. The study site will then obtain the patient's identification number and treatment assignment from the IVRS. Randomization to one of the two treatment arms will occur in a 1:1 ratio . Patients must receive their first dose of study drug within 1–3 days of being randomized.

The investigator and the patient will be blinded to treatment assignment. Following disease progression, patients previously randomized to erlotinib + placebo will be given the option to receive MetMAb, in addition to continuing erlotinib, provided that they continue to meet eligibility criteria (except for prior EGFR exposure).

Unblinding of treatment assignment prior to documented radiographic disease progression is permitted only for a serious, unexpected study drug–related toxicity (as part of safety reporting process). All individual requests for safety unblinding require the approval of the Medical Monitor.

The investigator may hold administration of study drug while waiting for a decision on unblinding to be made.

Erlotinib has a median terminal half-life of 3.43 to 9.07 hours. There is no available antidote to erlotinib; any toxicity associated or possibly associated with erlotinib treatment should be managed according to Table 2.

MetMAb has a half-life of approximately 10 days. Discontinuation of MetMAb will have no immediate therapeutic effect. There is no available antidote to MetMAb. The investigator may hold administration of MetMAb while waiting for a decision on unblinding to be made. Any toxicity associated or possibly associated with MetMAb/placebo should be managed according to standard medical practice.

All requests for unblinding must be made by contacting the Medical Monitor directly during business hours. Approval of the request and unblinding of study treatment assignment will occur only during business hours.

4.3 STUDY TREATMENT

4.3.1 Trial Drug

a. Formulation

MetMAb will be supplied as a sterile liquid in a single-use 15-cc vial.
Each vial contains 600 mg of MetMAb in 10 mL at a concentration of 60 mg/mL in 10 mM histidine acetate, 120 mM trehalose, 0.02% polysorbate 20, pH 5.4.

Placebo will consist of 250 cc 0.9% NSS (Saline IV solution, 0.9%) and will be provided by the investigative site.

Erlotinib oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. In addition to the active ingredient (erlotinib), tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and magnesium stearate.

Tablets containing 25 mg, 100 mg, and 150 mg of erlotinib are available.

b. Dosage, Administration, and Storage

MetMAb will be administered as an IV infusion. The total dose of MetMAb for each patient will be 15mg/kg in 250 cc final 0.9% NSS. The weight at screening will be used to determine the actual dose of MetMAb. This dose will be administered throughout the study and will not change according to weight.

Active study drug will be administered intravenously, after dilution in normal saline (0.9%). The volume of MetMAb to be given will be calculated for each patient. A volume of sterile saline equal to the calculated volume of MetMAb from the vial will be withdrawn from the normal saline IV bag and discarded. The calculated volume of study drug will be drawn into a syringe and injected into the normal saline IV bag. Mix the IV bag by gently inverting after injecting the study drug, do not shake. Once MetMAb has been diluted, it must be used within 8 hours. *If diluted MetMAb needs to be transported to another facility, it should be diluted in PVC bags and transported at 5°C.*

The 250-cc final volume of 0.9% NSS containing MetMAb/placebo infusion will be administered over 60 (± 10) minutes as a continuous IV infusion on Day 1 of the first four cycles. Patients will be observed for approximately 60 minutes after completion of the infusion for fever, chills, or other infusion-associated symptoms. After the first four cycles, the MetMAb/placebo infusion may be delivered over 30 (±10) minutes, provided the patient tolerated the previous 4 infusions.

Upon receipt, vials containing MetMAb must be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. Vials used for one patient may not be used for any other patient. VIALS ARE FOR SINGLE USE ONLY. Any remaining solution should be discarded. Dextrose should not be used for dilution of MetMAb.

The dose of erlotinib will be 150 mg by mouth (PO) daily (QD). Dosing of erlotinib on the days of the MetMAb/placebo infusion will be done in the clinic. This dose may be reduced as outlined in under "Dosage Modification" below. Tablets should be taken preferably in the morning with approximately 200 mL water, at least 1 hour before or 2 hours after a meal.

Patient compliance in taking the assigned erlotinib daily dose will be assessed by standard pill counts. Bottles and blister packages containing erlotinib tablets will be given to patients at regularly scheduled visits. Previously distributed bottles and blister packages will be returned to the clinic and counted; discrepancies will be resolved with the patient at each clinic visit and documented in the patient's medical chart.

Erlotinib has only been studied in patients over the age of 18 years. Current data do not show a need for a different initial dose in elderly populations.

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

Infusion Modification

The MetMAb/placebo infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. If infusion-related symptoms occur, patients will be treated according to best medical practice and will be monitored until adequate resolution of signs and symptoms. Study treatment will be

administered in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. Patients who experience MetMAb/placebo infusion–associated symptoms may be pre-medicated appropriately (e.g., with NSAIDS, acetaminophen and/or diphenhydramine for subsequent infusions). The use of any steroids requires *prior* approval by the Medical Monitor. Please refer to Section 5 for additional information regarding the management of adverse events related to MetMAb.

Infusion Schedule Modification

If a treatment interruption is required, MetMAb/placebo dosing may be delayed by up to 7 days (dose delays longer than 7 days may be considered pending discussion with the Medical Monitor). If a patient has required two dose delays for the same adverse event and within the first four cycles, the patient may continue dosing on a 28-day cycle, pending discussion with the Medical Monitor. If a scheduled dosing coincides with a holiday that precludes dosing, dosing should commence on the nearest following date and subsequent dosing should continue on a 21-day schedule.

Dosage Modification

No modification of the MetMAb/placebo dose will be allowed during this study.

Dose reduction or interruption of erlotinib for toxicity likely attributable to erlotinib (e.g., rash, diarrhea) may take place at any time during the study. Dose interruptions should not exceed more than approximately 7 consecutive days. Dose level reductions are presented in Table 1. If a patient does not tolerate erlotinib at 50 mg, then *erlotinib* treatment should be discontinued*; the patient may continue on MetMAb/placebo, at the discretion of the investigator, following consultation with* the Medical Monitor. *Patients may continue on single-agent MetMAb (as randomized) if discontinuation of erlotinib is required because of tolerability issues, upon discussion with the Medical Monitor.*

Table 1
Erlotinib Dose Reduction

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

Management of Toxicities Related to Study Treatment

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

Table 2

Erlotinib Dosage Modification Criteria and Guidelines for Management of 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 q 2–4 hours until free of diarrhea for 12 hours).
Grade 2	None. (Dose reduction of erlotinib is necessary if diarrhea persists over 48–72 hours despite optimal medical management.)	Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours).
Grade 3	Interrupt erlotinib.	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours). Interrupt erlotinib until resolution to Grade ≤ 1, and restart at next reduced dose.
Grade 4	Discontinue erlotinib and contact the Medical Monitor.	Per best medical practice
Pulmonary events		
All Grades	Temporarily interrupt erlotinib pending the diagnostic evaluation. If the pulmonary adverse event is assessed as related to erlotinib, discontinue the patient from the study drug to which it is assessed as related.	Unexplained pulmonary symptoms, either new or progressive, should be aggressively evaluated.
Rash		
Tolerable rash	None.	Any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course) at discretion of investigator
Intolerable rash	Interrupt erlotinib (no more than ~7 consecutive days); Restart erlotinib at same dose; if rash persists/worsens, reduce erlotinib dose	Manage as described above.
Grade 4	Discontinue erlotinib and contact the Medical Monitor.	Manage as described above.

Table 2 (cont'd)
Erlotinib Dosage Modification Criteria and Guidelines for Management of Toxicities

NCI CTCAE Grade	Study Drug Dose Modification	Guideline for Management
Hepatotoxicity		
Total bilirubin >3× upper limit of normal	Discontinue erlotinib and contact the Medical Monitor.	Per best medical practice
Transaminases >5× upper limit of normal	Discontinue erlotinib and contact the Medical Monitor.	Per best medical practice
Ophthalmic events		
Grade 3 conjunctivitis and keratitis	Discontinue erlotinib and contact the Medical Monitor.	Per best medical practice

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

All concomitant treatments (medications or procedures) within the 14 days preceding the initial study drug infusion on this study through Cycle 4 will be recorded; after hat, any new concomitant treatments and any changes to the daily dosing will be recorded as part of the targeted history/physical examination. The reason(s) for reatment, dosage, and dates of treatment will be reported to the investigator and ecorded as instructed on the study-specific case report form (CRFs).

- Patients should receive full supportive care, including hematopoietic growth factors, transfusions of blood and blood products, antibiotics, etc., when appropriate
- Appropriate prophylactic anti-emetic regimens should be provided to all patients who develop ≥ Grade 2 nausea and vomiting
- Patients who experience infusion-associated symptoms may be treated as clinically indicated, including ≤ 48 hours of treatment with corticosteroids. Pre-medication other than acetaminophen, NSAIDS, or diphenhydramine must be discussed with the Medical Monitor.

  If use of steroids is required, it is recommended that the dosing remains stable between the time of the two FDG-PET scans because steroid use may result in increased blood glucose levels, which would affect FDG uptake and potentially lead to a false assessment of PET response.

- 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 erlotinib and warfarin, it is preferable that patients not use warfarin for this purpose.
- Other medication considered necessary for the patient's safety and well-being may be given at the discretion of the investigator(s).
- Because erlotinib is metabolized by the CYP3A4 pathway, agents known to inhibit or induce CYP3A4 function may alter the pharmacokinetics of erlotinib. Although caution and careful monitoring are recommended when use of these compounds is necessary, usage does not exclude patient participation in this trial.
- Use of systemic corticosteroids for the treatment of skin toxicities is discouraged.

4.4.2 Excluded Therapy

The following therapies are 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

  Palliative radiation for bone metastases or other oncology-related issues may be considered, pending discussion with the Medical Monitor
- Systemic retinoids should not be given, because of theoretical concerns regarding a negative effect on the erlotinib mechanism of action

4.5 STUDY ASSESSMENTS

4.5.1 Definitions of Select Study Assessments

a. Tumor Assessments

Tumor assessments will be performed at Day 15–21 for Cycles 2, 4, 7, and every 3 cycles thereafter (i.e., Cycles 10, 13, 16, etc.), and at the Study Drug Discontinuation Visit (SDDV). Tumor assessments must be conducted prior to the next cycle of MetMAb/placebo. Objective response should be confirmed by repeat assessments ≥4 weeks after initial documentation.

The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study (e.g., the same contrast protocol for CT scans).

b. Unblinding upon Disease Progression and Treatment Crossover

A 20% increase in the sum of the longest diameter of target lesions constitutes progressive disease for the purposes of the primary endpoint of this study. However, upon the discretion of the investigator and the patient, where a 20% increase in the sum of the longest diameter of the target lesions is less than a 5 mm absolute increase, patients may be allowed to continue on assigned blinded therapy.

Following disease progression, patients randomized to the erlotinib + placebo arm will be given the option to receive MetMAb (in addition to continuing erlotinib), provided they continue to meet the following eligibility criteria:

- ECOG performance status of 0, 1, or 2 (see Appendix D)
- Use of an acceptable means of contraception for men and women of childbearing potential
- No untreated and/or active (progressing or requiring anticonvulsants or corticosteroids for symptomatic control) CNS metastasis

Treatment with MetMAb + erlotinib should begin within 28 days of the date where disease progression was documented. *Treatment with erlotinib should continue while a decision about unblinding is being made.*

The same "treatment phase" schedule of assessments and procedures will apply to the patients who have MetMAb added to erlotinib, following progression on erlotinib monotherapy, i.e., patients will begin on Cycle 1 (now to be called Cycle 1A) and will follow the same assessments and procedures as outlined in this protocol *including pharmacokinetic and pharmacodynamic sampling* (with the exception of FDG-PET imaging, which will not be requested in these patients) for this and all subsequent cycles (i.e., Cycle 2, which will now be called Cycle 2A, etc.).

c. Required Tissue Samples

A formalin-fixed, paraffin-embedded tumor specimen that enabled the definitive diagnosis of NSCLC with either adequate viable tumor cells in a tissue block (preferred) or 15 unstained, serial slides, accompanied by an associated pathology report, is required prior to randomization. Cytological *or fine-needle aspiration* samples are not acceptable. If the archival tissue is neither sufficient nor available, the patient may still be eligible, upon *prior* discussion with the Medical Monitor, assuming the patient can provide at least ≥5 unstained,

serial slides or is willing to consent to and undergo a pre-treatment *core or excisional* biopsy *(fine-needle aspiration is not allowed)* of the NSCLC tumor.

d. Laboratory Tests/Other Evaluations

The following tests are to be performed by a local laboratory unless otherwise noted:

- Hematology: red blood cell (RBC), white blood cell (WBC), hemoglobin, hematocrit, platelets, WBC *five-part* differential count (neutrophils, bands *[separate from neutrophils]*, lymphocytes, eosinophils, basophils, and monocytes), ANC, PT, and INR
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test at screening. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

All patients with clinically significant abnormal laboratory results are to be followed until the results return to normal ranges or until a valid reason, other than a drug-related adverse event, is identified.

e. Smoking History

Patients will need to be categorized for stratification as 1) non-smokers (or those who have smoked less than 100 cigarettes in a lifetime) versus 2) current/former smokers.

f. Concomitant Medications

Documentation of concomitant medications (includes prescription medications and over-the-counter preparations) used by the patient during the 14 days prior to Cycle 1, Day 1, during the study and at the end of the study at the Study Drug Discontinuation Visit.

g. Physical Exams

A complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, gynecologic, and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical

examination. New or worsened abnormalities should be recorded as adverse events if appropriate. A targeted physical exam includes asking the patient about changes from the previous exam and includes investigating any new abnormalities.

h. Follow-up Assessment for Survival

Survival follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, loss to follow-up, study treatment termination, or study termination by Genentech.

Please refer to Appendices A and B (study flowcharts) for a complete schedule of study assessments.

4.5.2 Screening and Pretreatment Assessments

Informed consent must be obtained before study-specific screening evaluations are performed and must be documented in the patient medical chart.

After informed consent has been obtained and eligibility has been established, the study site will be required to fax to the Medical Monitor information regarding the patient's eligibility; the archival diagnostic tissue or fresh tumor biopsy sample must be available at the site prior to randomization. The study site will obtain the patient's identification number and treatment assignment from the IVRS. Patients must receive their first dose of study drug within 3 days of being randomized. Local laboratories will perform all laboratory evaluations.

Please see the Study Flowcharts provided in Appendices A and B for the schedule of screening and pretreatment assessments.

Within 28 Days Prior to Day 1

- Obtain signed Informed Consent Form(s) as applicable
- Demographics, medical history and smoking history

  Smoking history; patients will be stratified according to smoking status

  Record height and weight
- Pregnancy test

  Serum or urine pregnancy test for all females of childbearing potential

  Document reason that patient is deemed not to be of childbearing potential in medical history for every female patient not administered a pregnancy test

- Required tissue samples available at the site (must be either located at the site or sent to the site from a referring institution)

  A formalin-fixed, paraffin-embedded tumor specimen that enabled the definitive diagnosis of NSCLC with adequate viable tumor cells in a tissue block (preferred) or 15 unstained, serial slides, accompanied by an associated pathology report, is required prior to randomization. Cytological *or fine-needle aspiration* samples are not acceptable. If the archival tissue is neither sufficient nor available, the patient may still be eligible, upon discussion with the Medical Monitor, assuming the patient can provide at least ≥5 unstained, serial slides or willing to consent to and undergo a pre-treatment *core or excisional* biopsy of the NSCLC tumor.

- Perform 12-lead electrocardiogram
- Obtain chest X-ray if chest CT is not performed within the radiographic assessment of disease sites
- Brain CT scan/MRI
- Perform a radiographic assessment *(CT/MRI)* of *the chest, abdomen, and pelvis*, using RECIST *1.0*

  Tumor burden must be evaluated by physical examination and image-based evaluation. Assessments *must* include *the chest, abdomen, and pelvis as well as* an evaluation of all sites of disease.

  The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study (e.g., spiral CT with IV contrast).

- Assess disease stage according to Tumor/Node/Metastases (TNM) staging system for lung cancer
- Optional DNA blood sample collected anytime after optional DNA informed consent has been signed

Within 14 Days Prior to Day 1

- Perform screening FDG-PET scan

  Pre-FDG-PET blood glucose test (for patients undergoing FDG-PET)

  Blood glucose levels will be obtained immediately prior to FDG administration either by fingerstick test or by serum glucose assay on a blood sample obtain by venipuncture and processed in the local laboratory. Patients should not have consumed food for 4 hours prior to this test.

  FDG-PET scans should not be obtained <7 days following a tumor biopsy, or any surgical procedure, unless the procedure involves a site that is not a region of interest (ROI) for FDG-PET imaging or a known target lesion on CT scan. *Management of elevated blood glucose is outlined in the imaging manual.*

- Optional exploratory PD (serum and plasma) sample collected anytime during the screening period after the optional sample informed consent has been signed and the patient has agreed to donate these samples (see Appendix B)
- Record all concomitant medications taken within 14 days of Cycle 1, Day 1
- Perform complete physical examination
- Take vital signs (heart rate, blood pressure, and temperature)
- Record ECOG performance status
- Perform the following laboratory assessments

  CBC: red blood cell (RBC), white blood cell (WBC), hemoglobin, hematocrit, platelets, WBC *five-part* differential count (neutrophils, bands *[separate from neutrophils]*, lymphocytes, eosinophils, basophils, and monocytes), ANC, PT, and INR

  Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase

4.5.3 Assessments during Treatment

Please see the Protocol Section 4.5.1 and the Study Flowchart provided in Appendices A and B for the schedule of treatment period assessments.

a. Cycle 1, Day 1

- Randomization (may occur 3 day prior to or on Day 1)

  The archival tissue and an associated pathology report must be confirmed to be available at the site (must be located at the site or sent to the site from a referring institution) prior to randomization.

b. Cycles 1–4

Day 1

- Targeted history/physical examination (ask the patient about changes from the previous exam and investigate any new abnormalities)
- Record adverse events
- Vital signs (blood pressure, heart rate, and temperature)
- Concomitant medications (record only changes to dosing schedule of previous concomitant medications or any new medications)
- ECOG performance status

- Perform the following laboratory assessments

  CBC: red blood cell (RBC), white blood cell (WBC), hemoglobin, hematocrit, platelets, WBC *five-part* differential count (neutrophils, bands *[separate from neutrophils]*, lymphocytes, eosinophils, basophils, and monocytes), ANC

  Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase

- Pre-dose serum and pre-dose plasma PK samples (including ATA serum sample collected pre-dose)
- Collect exploratory PD plasma sample (pre-dose)
- Collect separate PK sample (for AAG)
- Dispense erlotinib bottle(s) and instruct patient regarding the administration of erlotinib: orally, daily for 21 days each cycle

  Patients should take erlotinib with 200 mL of water at least 1 hour before or 2 hours after a meal before MetMAb/placebo infusion in the clinic. All subsequent doses should be taken in the morning with up to 200 mL of water at least 1 hour before or 2 hours after a meal.

- Administer MetMAb/placebo by infusion and record time of start and stop of infusion
- Collect the post-dose serum sample (approximately 1 hour post-infusion) and record time of collection
- Collect the post-dose plasma sample (approximately 2–4 hours post-erlotinib administration) and record time of collection
- Collect the post-dose PD plasma and serum samples (only for Cycle 1)

Day 8

- Targeted history/physical examination (ask the patient about changes from the previous exam and investigate any new abnormalities)
- Record adverse events
- Vital signs (blood pressure, heart rate, and temperature)

- Perform the following laboratory assessments

  CBC: red blood cell (RBC), white blood cell (WBC), hemoglobin, hematocrit, platelets, WBC *five-part* differential count (neutrophils, bands *[separate from neutrophils]*, lymphocytes, eosinophils, basophils, and monocytes), ANC

  Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase

Day 10–14 (Cycle 1 only)

- Pre-FDG-PET blood glucose test

  Blood glucose levels will be obtained immediately prior to FDG administration either by fingerstick test or by serum glucose assay on a blood sample obtain by venipuncture and processed in the local laboratory. Patients should not have consumed food for 4 hours prior to this test.

- FDG-PET study

  A FDG-PET scan should be performed if the patient has a pre-treatment FDG-PET scan with an evaluable lesion detected on the that FDG-PET scan. Procedures for obtaining FDG-PET scans are described in detail in the Imaging Charter

- Collect optional PD, serum and plasma PK sample (at time of FDG-PET $\pm$3 hours)

Day 15 (for the first 12 patients only and for Cycles 1 and 2 only)

- Targeted history/physical examination (ask the patient about changes from the previous exam and investigate any new abnormalities)
- Record adverse events
- Vital signs (blood pressure, heart rate, and temperature)
- Perform the following laboratory assessments

  CBC: red blood cell (RBC), white blood cell (WBC), hemoglobin, hematocrit, platelets, WBC *five-part* differential count (neutrophils, bands *[separate from neutrophils]*, lymphocytes, eosinophils, basophils, and monocytes), ANC

  Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase

Day 15–21 (Cycles 2 and 4 only)

- Tumor assessments, according to RECIST *1.0*, should be performed at Day 15–21. Tumor burden must be evaluated by physical examination and image-based evaluation. Assessments should include an evaluation of all sites of disease. The same radiographic procedure must be used throughout the study for each patient. Objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation.

Cycles 2–4

Day 1

- Collect optional exploratory PD plasma sample (pre-dose)

Cycles ≥5

Day 1

- Targeted history/physical examination (ask the patient about changes from the previous exam and investigate any new abnormalities)
- Record adverse events
- Vital signs (blood pressure, heart rate, and temperature)
- Concomitant medications (record only changes to dosing schedule of previous concomitant medications and any new medications)
- ECOG performance status
- Perform the following laboratory assessments

  CBC: red blood cell (RBC), white blood cell (WBC), hemoglobin, hematocrit, platelets, WBC *five-part* differential count (neutrophils, bands *[separate from neutrophils]*, lymphocytes, eosinophils, basophils, and monocytes), ANC

  Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase
- Pre-dose serum PK sample (including ATA serum sample collected pre-dose); these should be collected every four cycles after Cycle 4 (i.e., Cycle 8, 12, 16, etc)
- Dispense erlotinib bottle(s) and instruct patient regarding the administration of erlotinib: orally, daily for 21 days each cycle

  Patients should take erlotinib with 200 mL of water at least 1 hour before or 2 hours after a meal before MetMAb/placebo infusion in the clinic. All subsequent doses should be taken in the morning with up to 200 mL of water at least 1 hour before or 2 hours after a meal.

- Administer MetMAb/placebo by infusion and record time of start and stop of infusion

Day 15–21 (Cycle 7 and every 3 cycles thereafter [i.e., Cycles 10, 13, 16, etc.])

- Tumor assessments, according to RECIST *1.0*, should be performed at Day 15–21. The same radiographic procedure must be used throughout the study for each patient. Objective response should be confirmed by repeat assessments ≥4 weeks after initial documentation.

Additional visits/labs should be scheduled according to best medical practices.

4.5.4 Study Drug Discontinuation Visit

Patients who are discontinued from study drug should return for a study drug discontinuation visit. This visit should occur *within* approximately 30 days after the completion of the treatment phase or the decision to discontinue treatment. The following evaluations and procedures will be preformed at the study drug discontinuation visit:

- Targeted history/physical examination (ask the patient about changes from the previous exam and investigate any new abnormalities)
- Record adverse events
- Vital signs (blood pressure, heart rate, and temperature)
- ECOG performance status
- 12-lead electrocardiogram
- Concomitant medications
- Obtain chest X-ray*, if warranted*
- Biopsy sample upon disease progression will be requested from all patients who have provided consent (optional)
- Perform the following laboratory assessments:

  CBC: red blood cell (RBC), white blood cell (WBC), hemoglobin, hematocrit, platelets, WBC *five-part* differential count (neutrophils, bands *[separate from neutrophils]*, lymphocytes, eosinophils, basophils, and monocytes), ANC, PT and INR

  Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase

- Serum and plasma PK samples (including ATA serum sample)
- Collect exploratory PD plasma sample

  If the patient terminates study for reasons other than radiographic progression, every effort should be made to obtain a CT scan.

4.5.5 Follow-Up Assessments

a. Survival Follow-Up Assessments

Survival follow-up information will be collected via telephone calls and/or clinic visits approximately every 3 months *from last study visit* until death, loss to follow-up, or study termination by Genentech. All patients will be followed for survival information unless the patient requests to be withdrawn from study survival follow-up; this request must be documented in the source and signed by the investigator. If the patient withdraws from the study treatment but not from study follow-up, the study staff may use a public information source (like county records) to obtain information about survival status only.

b. Additional Safety Follow-Up

Patients who experience a Grade 4 or serious adverse event at treatment completion or at study drug discontinuation will be contacted by the investigator or his or her designee to determine the status of the event until the event is resolved or determined stable by the investigator.

Please see the Study Flowchart provided in Appendix A for specified follow-up assessments.

4.5.6 Requirement of FDG-PET Detectable Lesions

Patients are required to have a detectable lesion on a pre-treatment FDG-PET scan that is also a target lesion on CT according to RECIST *1.0* in order to qualify for this study. *Throughout* the *course of this study*, an *Image Reading Facility (*IRF*)* will *evaluate* FDG-PET *results* and *together with the Sponsor* will determine whether FDG-PET imaging *should continue in all participating sites or whether FDG-PET imaging should be confined to a few sites based on the quality of the data received according to defined criteria.* Should the IRF *and the Sponsor* determine that FDG-PET scanning continue only at certain sites, then the eligibility criterion regarding the FDG-PET avid disease will only apply to the patients of those sites that will continue to perform FDG-PET imaging.

4.6 PATIENT DISCONTINUATION

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study; for reasons of noncompliance (e.g., missed doses, visits); if the patient becomes pregnant; or if the investigator determines it is in the best interest of the patient.

See Appendix A (Study Flowchart) for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

4.7 STUDY DISCONTINUATION

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.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

4.8 ASSAY METHODS

4.8.1 MetMAb Assay

Serum samples will be assayed for MetMAb in a direct sandwich ELISA. The assay will use murine anti-rhuMAb OA5D5 Complimentarity Determining Region (CDR) monoclonal antibodies in the capture phase and F(Ab')2 fragmented, goat anti-human IgG Fc antibodies conjugated to horseradish peroxidase will be used for detection. The minimum quantifiable concentration for this assay is 0.2 µg/mL.

4.8.2 Anti-Therapeutic Antibody Assay

MetMAb serum samples will be assayed for ATA in a DIG (Digoxin/Digoxigenin) assay. This assay is currently in development.

4.8.3 Erlotinib Assay

Plasma concentrations of erlotinib will be determined by using a validated liquid chromatography/mass spectrometry (MS)/MS assay. Assay ranges for erlotinib will be 1–1007 ng/mL. The limit of quantitation will be set at the concentration of the lowest non-zero standard (1 ng/mL) for each compound.

4.8.4 α1-Acid Glycoprotein Assay

The α1-acid glycoprotein assay (AAG) is a nephelometric immunoassay. It is based on the ability of anti-α1-acid glycoprotein antiserum to recognize and bind to α1-acid glycoprotein in solution. The binding of the antiserum to the α1-acid glycoprotein in the plasma samples results in the formation of immunocomplexes, which causes the scattering of light. The intensity of the scattered light, measured using a nephelometer, is proportional to the concentration of the relevant protein in the sample. From the response of the sample and those of a standard curve, the concentration of α1-acid glycoprotein in the sample can be determined. The validated lower and higher limits of quantitation are 0.0131 g/L and 0.419 g/L, respectively.

4.8.5 Immunohistochemistry in Fixed-Tissue Specimens

Submission of either a formalin-fixed paraffin-embedded tumor specimens or unstained paraffin slides (15 slides) of representative tumor will be required for all patients enrolled into the study. Formalin-fixed, paraffin-embedded tissue sections will be deparaffinized prior to antigen retrieval, blocking and incubation with primary anti-c-Met antibodies. Following incubation with secondary antibody and enzymatic color development, sections will be counterstained and dehydrated in series of alcohols and xylenes before coverslipping. More information is provided in the study manual.

4.8.6 Exploratory Analysis of Tissue Specimens

In addition to IHC, other molecular or proteomic markers related to HGF/Met or EGFR signaling may be examined on pre-treatment archival or fresh biopsies. Furthermore, an optional biopsy sample may be obtained (as per the study manual) from patients with disease progression, for the evaluation of mechanisms of erlotinib and/or MetMAb resistance.

For analysis of IL-8 protein expression, an Electrochemiluminescensce (ECL) based assay will be used (MesoScale Discovery, Gaithersburg, MD).
The dynamic range of the assay is from 2–2000 pg/mL. In healthy volunteers, levels of IL-8 appear to range from 8–20 pg/mL. HGF levels will be assessed using a proprietary ELISA based assay. The dynamic range of the assay is from 10–1000 pg/mL. In healthy volunteers, the level of HGF is ~600 pg/mL.

4.9 STATISTICAL METHODS

Primary and secondary efficacy analyses will include all randomized patients, with patients allocated to the treatment arm to which they were randomized.

Safety analyses will include all randomized patients who received at least one dose of study treatment, with patients allocated to the treatment arm associated with the regimen actually received.

4.9.1 Analysis of the Conduct of the Study

The number of patients who are randomized will be tabulated by study site and treatment arm. Eligibility exceptions and protocol deviations will be summarized by treatment arm. Patient disposition will be tabulated by treatment arm, and reasons for premature discontinuation will be summarized.

4.9.2 Analysis of Treatment Group Comparability

Demographic and baseline characteristics (e.g., age and sex) will be summarized using means, standard deviations (SD), medians, and ranges for continuous variables, and proportions for categorical variables, as appropriate. Summaries will be presented *by "overall" patient population* and by treatment arm. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

4.9.3 Efficacy Analyses

a. Primary Efficacy Endpoint

Kaplan–Meier methodology will be used to estimate the median PFS for each treatment arm. The stratification factors will be determined by the CRF data, not by data collected by the IVRS at the time of randomization unless the CRF data is missing. Estimation of the hazard ratio (i.e., the magnitude of treatment effect and 95% confidence interval) will be determined using a stratified Cox regression model with an indicator variable for MetMAb treatment.

The same analysis methods as those described for PFS in *"overall" population* patients are applied to *patients with Met* positive *tumors and to patients with SCC histology*. All deaths from any cause within 30 days of the last treatment will be included as PFS events.

b. Secondary Efficacy Endpoints

Objective response is defined as a complete or partial response determined on two consecutive occasions ≥ 4 weeks apart. Patients without a post-baseline tumor assessment will be considered non-responders. An estimate of the objective response rate and 95% confidence intervals (Blyth–Still–Casella) will be calculated for each treatment arm. Confidence intervals for the difference in tumor response rate (Satner and Snell 1980; Berger and Boos 1994) will be calculated.

For patients with an objective response, duration of objective response is defined as the time from the initial response to disease progression or death from any cause within 30 days of the last treatment. Methods for handling censoring and for analysis are the same as described for PFS. *All secondary efficacy endpoints will be assessed for patients with MET positive tumors, patients with SCC histology, and by "overall" patient population.*

c. Exploratory Efficacy Endpoints

Overall survival is defined as the time from randomization until death from any cause. All deaths will be included, whether they occur on study or following treatment discontinuation. For patients who have not died, overall survival will be censored at the date of last contact. As patients in the erlotinib + placebo arm may cross over to erlotinib + MetMAb, crossover analysis will be applied and overall survival will be used as time-varying covariates in the analysis.
All exploratory efficacy endpoints will be assessed for patients with MET positive tumors, patients with SCC histology, and by "overall" patient population.

4.9.4 Safety Analysis

Safety will be assessed through summaries of adverse events, laboratory test results, and immunogenicity as measured by ATA. Summaries will be presented by treatment arms. Safety analyses will include all patients who receive any amount of study treatment.

a. Laboratory Data

Changes in NCI grade will be tabulated by treatment arm, and Grade 3 and 4 laboratory data will be listed.

b. Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be mapped to the appropriate thesaurus terms and summarized by mapped term, appropriate thesaurus level, and NCI CTCAE grade. For each patient's adverse event, the maximum severity reported will be used in the summaries. Serious adverse events, including deaths, will be summarized separately.

c. Anti-Therapeutic Antibody

ATA results will be assessed and listed by patient and cycle.

4.9.5 Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean concentration versus time data will be tabulated for MetMAb, erlotinib, and AAG. Mean plots by dose level will be generated for both MetMAb and erlotinib.

The measured concentration values will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Inter-patient variability and drug accumulation will be evaluated.

MetMAb serum concentrations at all measured timepoints will be compared with simulated results based on PK data collected in a Phase I study (OAM4224g, A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacology of Metmab [Pro143966], a Monovalent Antagonist Antibody to the Receptor C-Met, Administered Intravenously in Patients with Locally Advanced or Metastatic Solid Tumors). Erlotinib plasma concentrations at all measured timepoints will be compared with simulated results based on previous population pharmacokinetic analyses (Report 04-0143-1219: Population Pharmacokinetics of Erlotinib: An Abbreviated Population Analysis Using Single-Agent Data, Including Study BR.21).

Additional PK and PD analyses will be conducted as appropriate.

4.9.6 Handling of Missing Data

For PFS, data for patients who are lost to follow-up will be treated as censored on the last date the patient was known to be progression free. Data for patients who are randomized and not treated and who do not have any post-randomization tumor assessments will be treated as censored on the randomization day plus 1 day.

For survival, data for patients who are lost to follow-up will be treated as censored on the last date the patient was known to be alive. This may be the randomization date plus 1 day for patients who are randomized, not treated, and immediately lost to follow-up.

For objective response, patients without a post-baseline tumor assessment will be counted as a non-responder.

4.9.7 Determination of Sample Size

This Phase II trial is designed to make a preliminary assessment of the safety and activity of MetMAb+erlotinib in patients with NSCLC who have relapsed following one or two prior regimens; special attention is given to outcomes in patients with Met positive tumors *and patients with squamous cell histology.* The study will *initially* accrue *approximately*120 *histologically unspecified ("overall" population)* patients; it is expected that about 50% of the enrolled patients (30 per arm) *will* have Met positive tumors by IHC. *For evaluation of the primary endpoint, p*atients will be followed *until the time of* approximately *42* investigator-assessed PFS events among patients with Met positive tumors *in the "overall" population. In addition, this study will accrue approximately 80 total SCC patients (approximately 30 in the "overall" population, followed by accrual of approximately 50 subsequent SCC patients). A PFS analysis among patients with squamous histology will occur when approximately 55 investigator-assessed PFS events have been observed.*

This Phase II trial is hypothesis-generating and is able to detect only a large benefit of combination therapy with MetMAb+erlotinib. For example, with 42 events in patients with Met-positive tumors, there is 80% power to detect, at a one-sided significance level of 0.025, an HR of 0.4 in MetMAb+erlotinib, compared with erlotinib+placebo. This trial however, will not have adequate power to detect minimum clinically meaningful differences between the treatment arms. For example, there is only 21% of power to detect an HR of 0.7. Thus, formal hypothesis testing is limited in that statistically negative outcomes do not necessarily rule out clinically significant treatment effects.

4.10 DATA QUALITY ASSURANCE

The data will be collected via Electronic Data Capture (EDC) using eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The CRO will be responsible for the data management of this trial, including quality checking of the data.

Genentech will perform oversight of the data management of this trial. Genentech will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central Laboratory and IRF data will be sent directly to Genentech, using Genentech's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Genentech and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology and clinical chemistry 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).

The safety of erlotinib + placebo and of erlotinib + MetMAb will be assessed through collection and analyses of adverse events (AEs) and serious adverse events (SAEs), baseline medical conditions, laboratory tests, and vital sign data.

Genentech or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Genentech or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days

after being notified of the event. Genentech or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

5.1.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) 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)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies, medication washout, or no treatment run-in).
- Preexisting medical conditions (other than non–small cell cancer), judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

5.1.2 Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- 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)

- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (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 **non-serious AEs**.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory 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 vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

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

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 5.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

5.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of study medications (the Genentech product(s) or other IMP), all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see Section 5.6).

5.2.2 Eliciting Adverse Events

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

> "How have you felt since your last clinic visit?"
>
> "Have you had any new or changed health problems since you were last here?"

5.2.3 Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the appropriate AE/ eCRF page.

For each AE and SAE recorded on the AE eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity and causality.

The AE grading (severity) scale found in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0 will be used for assessing AE severity.

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	

The NCI CTCAE v3.0 can be found: http://ctep.cancer.gov/reporting/ctc_v30.html

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

[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 causality assessments, investigators should apply the following general guidelines:

Table 4
Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

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 RECORDING ADVERSE EVENTS

5.3.1 Recording Adverse Events on the eCRF

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

Only one medical concept should be recorded in the event field on the AE eCRF page.

a. Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF 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 eCRF. 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 eCRF.

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

c. Persistent or Recurrent Adverse Events

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

A recurrent AE/SAE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an AE eCRF page.

d. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

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 eCRF 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 eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term 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 eCRF, unless their severity, seriousness, or etiology changes.

e. Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 5.2.1) that are attributed by the investigator solely to progression of non–small cell lung cancer will be recorded only on the Study Discontinuation eCRF page. All other on-study deaths, regardless of attribution, will be recorded on an SAE eCRF page and expeditiously reported to the Sponsor.

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

During post-study survival follow-up, deaths attributed to progression of non–small cell lung cancer will be recorded only on the Survival eCRF page.

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 eCRF page.

A preexisting medical condition should be 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 eCRF page, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

g. Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an activity measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

h. Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 90 days after the last dose of investigational product, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department within 24 hours of learning of the pregnancy to facilitate outcome follow-up.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an SAE eCRF page, and expeditiously reported to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

5.4.1 Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

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 SAE eCRF page within 24 hours as described in Section 5.4.2.

Medical Monitor Contact Information for sites in the United States and Canada:

Medical Monitor:	Nancy Kivel, M.D. (CRO Medical Monitor)
Telephone No.:	+1 (781) 434-5480
Alternate Telephone No.:	+1 (781) 434-5010

Medical Monitor Contact Information for the sites in Europe:

Medical Monitor:	Theodor Schulte, M.D. (CRO Medical Monitor)
Telephone No.:	+49 30 30 685 274

Medical Monitor Contact Information for the sites in the Asia Pacific Region:

Medical Monitor:	*QingMei Shi*, M.D. (CRO Medical Monitor)
Telephone No.:	*+65 62209326 ext. 511*

5.4.2 Reporting Requirements for All SAEs

For all sites, investigators will submit reports of all SAEs, regardless of attribution, to Genentech (or designee) 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 an AE/SAE eCRF page and submit it electronically using the EDC system.

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

A report will be generated and sent to Genentech Drug Safety by the EDC system. In the event the EDC system is unavailable, a completed paper AE/SAE CRF reporting form and fax coversheet should be faxed immediately upon completion to Genentech's Drug Safety Department or its designee at the fax numbers provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Sites in the United States and Canada:

Fax No.:	+1 (650) 225-4682
Alternate Fax No.:	+1 (650) 225-5288

Sites in Europe:

Fax No.:	+49 30 30 685 177

Sites in the Asia Pacific Region:

Fax No.:	+8610 58797674
Alternate Fax No.:	+8610 58797672

Genentech or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating Investigators, in accordance with European Clinical Trials Directive (Directive 2001/20/EC), ICH guidelines, and/or local regulatory requirements.

Genentech or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug (expedited reports) to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Genentech or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs by a written safety report within 15 calendar days of notification.

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

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the appropriate AE/SAE eCRF page and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, Genentech 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).

5.6 POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify Genentech of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. Genentech should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety via the study SAE eCRF. If the study SAE eCRF is no longer available, the investigator should report the event directly to Genentech Drug Safety (or designee) via telephone (see telephone numbers in Protocol Section 5.4.1).

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Genentech or a Genentech representative:

- 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 sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current curricula vitae and evidence of licensure of the Principal Investigator and all sub-investigators
- Complete financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572
- Federalwide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form

  Genentech or its designee must review any proposed deviations from the sample Informed Consent Form.

- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable), IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- Canada only when applicable: original Qualified Investigator Undertaking Form, signed by each Canadian investigator involved in the study
- All documents as appropriate for conduct of a trial in the local region of the site.

6.2 STUDY COMPLETION

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
- All laboratory certifications for laboratories performing the analysis (is other than Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, 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 (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and sub-investigator, U.S. FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s) [if applicable]
- Updated financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORM

Genentech's Sample Informed Consent Form will be provided to each site. Genentech or its designee must review and approve any proposed deviations from the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to Genentech for regulatory purposes.

The Consent Forms 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 the informed consent process and that written informed consent was obtained prior to participation in the study. A copy

of each signed 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.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to Genentech for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

Optional Research Informed Consent

If archival tissue and/or plasma/serum collection for optional research described in Section 3.1 is approved by the IRB/EC, the Consent Form entitled "Sample Research Informed Consent Form," will be provided by Genentech to each study site. This form gives patients the option to authorize the collection and use of these samples and personal health information for additional research purposes. Signing of this separate consent form is not required for enrollment in the trial but is required prior to any optional research sample collection. All procedures outlined above for review, approval, processing, and use of Consent Forms also apply to this optional research form.

In the United States, each Informed Consent Form may also include authorization allowing the institution, investigator, sub-investigator and the Sponsor(s) to use and disclose Personal Health information in compliance with the HIPAA of 1996.

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

6.4 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Genentech. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

6.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Genentech representative to inspect study data, patients' medical records, and eCRFs. The Principal Investigator will permit Genentech monitors/representatives and collaborators, the U.S. FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the Medidata RAVE EDC system. Sites will receive training and a manual for appropriate eCRF completion. eCRFs will be submitted electronically to Genentech and should be handled in accordance with instructions from Genentech.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

6.7 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the eCRFs 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 entered into the eCRFs 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 the deletion or alteration of 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 Quality Assurance group may assist in assessing 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 must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

6.9 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

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

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, 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 ICH Guideline for GCP (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 eCRFs, 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.

No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech for transfer of any records to another party or moving them to another location.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

REFERENCES

Ayhan A, Ertunc D, Tok EC, et al. Expression of the c-Met in advanced epithelial ovarian cancer and its prognostic significance. Int J Gynecol Cancer 2005;15:618–23.

Baykal C, Ayhan A, Al A, et al. Overexpression of the c-Met/HGF receptor and its prognostic significance in uterine cervix carcinomas. Gynecol Oncol 2003;88:123–9.

Berger RL, Boos DD. P values maximized over a confidence set for the nuisance parameter. J Am Stat Assoc 1994;89:1012–6.

Birchmeier C, Birchmeier W, Gherardi E, et al. Met, metastasis and more. Nat Rev Mole Cell Biol 2003;4:915–25.

Boix L, Rosa JL, et al. c-Met mRNA overexpression in human hepatocellularcarcinoma. Hepatology 1994;19:88–91.

Bonine-Summers AR, Aakre, ME, Brown, KA, et al. Epidermal growth factor receptor plays a significant role in hepatocyte growth factor mediated biological responses in mammary epithelial cells. Cancer Biol Ther 2007;6:561–570.

Bottaro DP, Rubin JS, Faletto DL, et al. Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. Science 1991;251:802–4.

Bunn PA, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: A review of the literature and future directions. Clinical Cancer Research 1998;4(5):1087–1100.

Cheng HL, Liu HS, Lin YJ, et al. Co-expression of RON and MET is a prognostic indicator for patients with transitional-cell carcinoma of the bladder. Br J of Cancer 2005;92:1906–14.

Danilkovitch-Miagkova A, Zbar B. Dysregulation of Met receptor tyrosine kinase activity in invasive tumors. J Clin Invest 2002;109(7),863–867.

Engelman JA, Kreshnik Z, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039–1043.

Fisher OM, Giordano S, Comoglio PM, et al. Reactive oxygen species mediate Met receptor transactivation by G-protein-coupled receptors and the epidermal growth factor receptor in human carcinoma cells. Journal of Biological Chemistry 2004;279:28970–28978.

Gherardi E, Stoker M. Hepatocytes and scatter factor. Nature 1990;346:228.

Guo A, Villén J, Kornhauser J,,et al. Signaling networks assembled by oncogenic EGFR and c-Met. PNAS 2008; 105(2):692–697.

Ichimura E, Maeshima A, Nakajima T, et al. Expression of c-met/HGF receptor in human non-small cell lung carcinomas in vitro and in vivo and its prognostic significance. Jpn J Cancer Res 1996;87:1063–9.

Koocheckpour S, Jeffers M, Rulong S, et al. Met and hepatocyte growth factor/scatter factor expression in human gliomas. Cancer Res 1997;57:5391–8.

Ma PC, Maulik G, Christensen J, et al. c-Met: structure, functions and potential for therapeutic inhibition. Cancer Metastasis Rev 2003;22:309–25.

Masuya D, Huang C, Liu D, et al. The tumour-stromal interaction between intratumoral c-Met and stromal hepatocyte growth factor associated with tumour growth and prognosis in non-small-cell lung cancer patients. Br J Cancer 2004;90:1555–62.

Miyazawa K, Tsubouchi H, Naka D, et al. Molecular cloning and sequence analysis of cDNA for human hepatocyte growth factor. Biochem Biophys Res Commun 1989;163:967–73.

Nakamura T, Nishizawa T, Hagiya M, et al. Molecular cloning and expression of human hepatocyte growth factor. Nature 1989;342:440–3.

Patel JD. Epidermal Growth Factor Receptor pathway targeted therapy in patients with aerodigestive malignancies. Current Opinion in Oncology 2006;18(6), 609–614.

Prat M, Crepaldi T, Pennacchietti S. Agonistic monoclonal antibodies against the Met receptor dissect the biological responses to HGF. Cell 1998;111(Pt 2):237–47.

Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.

Santner T, Snell MK. Small-sample confidence intervals for p1-p2 and p1/p2 in 2 $\times$ 2 contingency tables. J Am Stat Assoc 1980;75:386–94.

Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543–51.

Schiller JH, Harrington D, Belani CP et al. Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–8.

Shepherd FA, Pereira J, Ciuleanu TE, et al. A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st-line or 2nd-line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTC) trial. J Clin Oncol 2004; 22(Suppl 14):7022.

Stoker M, Gherardi E, Perryman M, et al. Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. Nature 1987;327:239–42.

Turesson I, Abildgaard N, Ahlgren T et al. Prognostic evaluation in multiple myeloma: an analysis of the impact of new prognostic factors. Br J Haematol 1999;106:1005–12.

Uchida D, Kawamata H, Omotehara F, et al. Role of HGF/c-Met system in invasion and metastasis of oral squamous cell carcinoma cells in vitro and its clinical significance. Int J Cancer 2001;93:489–96.

Weidner KM, Arakaki N, Hartmann G, Vandekerckhove J, Weingart S, Rieder H, et al. Evidence for the identity of human scatter factor and human hepatocyte growth factor. Proc Natl Acad Sci USA 1991;88:7001–5.

Wu CW, Li AF, Chi CW, et al. Hepatocyte growth factor and Met/HGF receptors in patients with gastric adenocarcinoma. Oncol Rep 1998;5:817–22.

Zarnegar R, Michalopoulos G. Purification and biological characterization of human hepatopoietin A, a polypeptide growth factor for hepatocytes. Cancer Res 1989;49:3314–20.

Zucali PA, Ruiz MG, Giovannetti E. et al. Role of cMET expression in non-small-cell lung cancer patients treated with EGFR tyrosine kinase inhibitors. Annal of Oncology 2008;19(9):1605–1612.

APPENDIX A
Study Flowchart

Assessment or Procedure	Screening		Cycles 1–4				Cycles ≥5	SDDV [a]	FU
Day	−28 to Day 1	−14 to Day 1	1	8	10–14 (Cycle 1 only)	15	1		
Informed consent	x								
Randomization [x]			x						
Demographics and smoking history	x								
Medical history	x								
Complete physical examination		x							
Targeted history/physical examination			x	x		x[c]	x	x	
Adverse events			x	x		x[c]	x	x[l]	
Vital signs [d]		x	x	x		x[c]	x	x	
Weight and height	x								
ECOG performance status		x	x				x	x	
Pregnancy test (serum or urine) [k]	x								
12-lead ECG	x							x	
Brain CT scan/MRI	x								
Chest X-ray [e]	x							x	
Archival tumor tissue sample	x [x]							x[b]	
Tumor radiographic assessment of all known disease sites	*x* [z]					x[f]	x[f]	x[y]	
FDG PET scan		x[h]			x[h]				
CBC [i]		x	x	x		x[c]	x	x	

APPENDIX A (cont'd)
Study Flowchart

Assessment or Procedure	Screening		Cycles 1–4				Cycles ≥5	SDDV [a]	FU
Day	−28 to Day 1	−14 to Day 1	1	8	10–14 (Cycle 1 only)	15	1		
Serum chemistries [j]		x	x	x		x[c]	x	x	
PT and INR [g]		x						x	
Serum MetMAb PK [o]			x		x[u]		x[w]	x	
Anti-MetMAb antibody serum sample [n]			x				x[w]	x	
Plasma erlotinib PK [o]			x		x[u]			x	
AAG sample [n]			x						
Concomitant medications		x[m]	x				x	x	
Exploratory PD plasma sample		x	x		x[u]			x	
Exploratory PD serum sample		x	x		x[u]				
Optional DNA sample	x[p]								
Dispense/collect erlotinib [q]			x				x		
MetMAb/placebo administration (IV Q3 wks) [r]			x				x		
Follow-up assessment for survival [s]									x

CBC = complete blood count; FU = follow-up; IVRS = interactive voice response system; PK = pharmacokinetic; PD = pharmacodynamic; PO = oral; QD = daily; Q3 = every 3 weeks; SDDV = study drug discontinuation visit.

Note: Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] Performed within ~30 days after the last dose of study treatment.

[b] Fresh *core or excisional* biopsy sample upon disease progression will be requested from all patients who have provided consent (optional)

[c] This visit is only required for the first 12 patients enrolled on the study and only for the first two cycles. A ±2 day window will apply.

[d] Assessments are to be performed pre and post study drug infusion.

[e] Chest X-ray not needed if CT scan of the chest is performed as part of the tumor assessment during screening.

[f] Tumor assessments, according to RECIST *1.0*, should be performed at Day 15–21 of Cycles 2, 4, 7, and every 3 cycles thereafter (i.e., Cycles 10, 13, 16, etc.). The same radiographic procedure must be used throughout the study for each patient. Objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation.

[g] PT and INR sample will be processed by the local lab

[h] FDG-PET scanning is performed only at baseline and Day 10–14 of Cycle 1. FDG-PET scans should not be obtained <7 days following a tumor biopsy, or any surgical procedure, unless the procedures involves a site that is not a region of interest for FDG-PET imaging or a known target lesion on a CT scan. FDG-PET fasting glucose test will be obtained immediately prior to FDG administration either by finger stick test or by serum glucose assay.

[i] CBC including RBC, WBC, hemoglobin, hematocrit, platelets, ANC, WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes)

[j] Includes glucose, BUN, creatinine, sodium, potassium, chloride, phosphorus, magnesium, bicarbonate, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, AST, and ALT.

[k] For females of childbearing potential only; use a commercially available kit. A serum pregnancy test is only confirmatory and does not need to be performed for all female patients.

[l] Patients who have an ongoing Grade 4 or serious adverse event that is thought to be related to MetMAb/placebo at the treatment completion/early termination visit will be contacted by the investigator or his or her designee every 2 weeks until the event is resolved or determined to be irreversible by the investigator.

[m] At screening, collect all concomitant medications taken within 14 days prior to Day 1.

[n] Sample taken before study drug administration.

[o] PK samples for MetMAb and erlotinib will be collected. MetMAb samples will be collected pre-study drug administration and 1 hour (± 30 minutes) following the end of the infusion. Erlotinib PK samples will be collected pre-erlotinib administration and 2–4 hours post-erlotinib administration. PK samples will be collected for the first four cycles and at study termination.

[p] Optional DNA sample for future research for patients who sign the optional DNA Informed Consent Form. Can be collected at the same time as any regularly scheduled blood draw.

[q] Erlotinib will be dispensed after PK (serum and plasma) and blood draws. Erlotinib dosing should occur at the site on the days of scheduled PK draws.

[r] Study drugs should be administered in the following order: erlotinib (PO), followed by MetMAb/placebo.

[s] Survival follow-up information will be collected as stated in Section 4.5.5.

[t] Randomization can occur prior to Day 1 (approximately Day -3 to Day 1) and after the patient has met all eligibility criteria and Medical Monitor approval has been obtained.

[u] The PK/PD samples on the FDG-PET Day can be obtained ±3 hours of scan. The optional PD sample may be obtained on the Day 8 visit, if phlebotomist is not available at the FDG-PET imaging site.

[v] Applicable only for patients who have signed the informed consent (optional). A plasma sample should be collected on Cycle 1 Day 1 pre-dose and post-dose and on Cycles 2–4 Day 1 pre-dose.

[w] This sample should be collected pre-dose every four cycles, after Cycle 4 (i.e. Cycle 4, 8, 12, etc).

[x] The archival tissue and an associated pathology report must be confirmed to be available at the site prior to randomization.

[y] If the patient terminates study for reasons other than radiographic progression, every effort should be made to obtain a CT scan.

[z] *Baseline CT scan should include evaluation of chest, abdomen, and pelvis.*

APPENDIX B
Study Flowchart for PK/PD Blood Sample Collection

Sample		Screening Day −14 to Day 0	Cycle 1 Day 1	Cycle 1 Day 10–14	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle ≥5 Day 1	SDDV
Erlotinib PK (plasma)	Pre-study drug dose (erlotinib and MetMAb)		x		x	x	x		
	Pre-study drug dose (erlotinib and MetMAb) AAG sample		x		x	x	x		
	2–4 hours post erlotinib dose		x		x	x	x		
	During visit			x [b]					x
MetMAb PK (serum)	Pre-study drug dose (erlotinib and MetMAb)		x		x	x	x	x [c]	
	1 hour post MetMAb dose		x		x	x	x		
	During visit			x [b]					x
ATA [a] and optional PD sample (serum)	Pre-study drug dose (erlotinib and MetMAb)		x		x	x	x	x [c]	
	During visit	x	x [d]	x [b]					x
Optional PD (plasma) [a]	Anytime during visit	x		x [b]					x
	Pre-study drug dose (MetMAb and erlotinib)		x		x	x	x		
	1 hour post MetMAb dose		x						

PD = pharmacodynamic; SDDV = study drug discontinuation visit.

[a] This sample may also be used for exploratory PD analysis, if the patient has signed the informed consent

[b] Obtain sample ±3 h of FDG-PET. The optional PD sample may be obtained on Day 8 visit, if phlebotomist is not available at the FDG-PET imaging site.

[c] This sample should be collected every four cycles, after Cycle 4 (i.e., Cycles 8, 12, etc).

[d] This should be collected approximately 1 hour post MetMAb infusion.

APPENDIX C
Response Evaluation Criteria in Solid Tumors (RECIST *1.0*)

1. Introduction

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST *1.0*) are below.[1]

2. Measurability of Tumor Lesions at Baseline

2.1. Definitions

At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as 20 mm with conventional techniques or as 10 mm with spiral CT scan [see Section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter <20 mm with conventional techniques or $<$10 mm with spiral CT scan] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

(*Note*: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate. Please refer to the Introduction of this Appendix.)

[1] Therasse P, Arbuck SG, Eisenhauser EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.

2.2. Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

2.2.2. Chest X-ray. Lesions on chest X-rays are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. More details concerning the use of this method of assessment for objective tumor response evaluation are provided in Appendix I.[2]

2.2.3. CT and MRI. CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities usually require specific protocols. More details concerning the use of these methods of assessment for objective tumor response evaluation are provided in Appendix I.[1]

2.2.4. Ultrasound. When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

---

[1] See Appendix I of the Therasse et al. article.

Justifications for not using ultrasound to measure tumor lesions for objective response evaluation are provided in Appendix I.[3]

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

2.2.6. Tumor markers. Tumor markers alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical response when all tumor lesions have disappeared. Specific additional criteria for standardized usage of prostate-specific antigen and CA (cancer antigen) 125 response in support of clinical trials are being validated.

2.2.7. Cytology and histology. Cytologic and histologic techniques can be used to differentiate between partial response and complete response in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has c-Met criteria for response or stable disease.

Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). New techniques to better establish objective tumor response will be integrated into these criteria, when they are fully validated, to be used in the context of tumor response evaluation.

---

[3] See Appendix I of the Therasse et al. article.

3. Tumor Response Evaluation

3.1. Baseline Evaluation

3.1.1. Assessment of overall tumor burden and measurable disease.
To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as defined in Section 2.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

3.1.2. Baseline documentation of "target" and "nontarget" lesions.
All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

3.2. Response Criteria

3.2.1. Evaluation of target lesions. This section provides the definitions of the criteria used to determine objective tumor response for target lesions. The criteria have been adapted from the original WHO Handbook (3), taking into account the measurement of the longest diameter only for all target lesions: complete response—the disappearance of all target lesions; partial response—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease—at least a 20% increase in the sum of the longest

diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started. A 20% increase in the sum of the longest diameter of target lesions constitutes progressive disease for the purposes of the primary endpoint of this study. However, where a 20% increase in the sum of the longest diameter of the target lesions is less than a 5 mm absolute increase, patients may be allowed to continue on assigned blinded therapy.

3.2.2. Evaluation of nontarget lesions. This section provides the definitions of the criteria used to determine the objective tumor response for nontarget lesions: complete response—the disappearance of all nontarget lesions and normalization of tumor marker level; incomplete response/stable disease—the persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker level above the normal limits; and progressive disease—the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.[4]

(Note: Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel [or study chair]. Please refer to the Introduction of this Appendix).

3.2.3. Evaluation of best overall response. The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded

since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 3.5.1).[4] Table 1 provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

[4] Refer to the Therasse et al. article.

Table 1
Overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions

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

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.
- Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the complete response status).

3.2.4. Frequency of tumor re-evaluation. Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of Phase II studies where the beneficial effect of therapy is not known, follow-up of every other cycle (i.e., 6–8 weeks) seems a reasonable norm. Smaller or greater time intervals than these could be justified in specific regimens or circumstances.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the Phase II trial has, as a goal, the response rate or the time to an event (disease progression/death). If time to an event is the main endpoint of the study, then routine re-evaluation is warranted of those subjects who went off the study for reasons other than the expected event at frequencies to be determined by the protocol. Intervals between evaluations twice as long as on study are often used, but no strict rule can be made.

3.3. Confirmatory Measurement/Duration of Response

3.3.1. Confirmation. The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in nonrandomized trials where response is the primary endpoint. In this setting, to be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first c-Met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of stable disease, measurements must have c-Met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6–8 weeks) that is defined in the study protocol (see Section 3.5.3).[5]

(*Note*: Repeat studies to confirm changes in tumor size may not always be feasible or may not be part of the standard practice in protocols where progression-free survival and overall survival are the key end points. In such cases, subjects will not have "confirmed response." This distinction should be made clear when reporting the outcome of such studies.

[5] Refer to the Therasse et al. article.

APPENDIX D
ECOG Performance Status Scale

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

APPENDIX E
Anaphylaxis Precautions

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Tourniquet
- Oxygen
- Epinephrine 1:1000 solution for intravenous (IV) or endotracheal injection
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations.