CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125085/85

Trade Name: Avastin

Generic Name: Bevacizumab

Sponsor: Genentech Incorporated

Approval Date: October 11, 2006

Indications: For first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic nonsquamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel

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APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125085/85

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125085/85

OCT 1 1 2006

Genentech, Incorporated
Attention: Todd Rich, M.D.
Vice President, Clinical and Commercial Regulatory Affairs
1 DNA Way, MS #242
South San Francisco, CA 94080-4990

Dear Dr. Rich:

Your request to supplement your biologics license application for Bevacizumab to include a new indication for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel has been approved.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this indication.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct a postmarketing study as described in your letter of October 11, 2006, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70:

1. To submit an efficacy supplement containing the final study report, including summary analyses and primary datasets, and appropriate revised labeling describing the effect of overall survival in the entire population and by gender and age from the Hoffman-LaRoche-sponsored study, BO17704 "A Randomized, Double-Blind, Multicenter Phase 3 Study of Bevacizumab in Combination with Cisplatin and Gemcitabine Versus Placebo, Cisplatin and Gemcitabine in Patients with Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer Who Have Not Received Prior Chemotherapy". The protocol was submitted to BB-IND 7023 on February 13, 2006, and patient accrual was completed by August 31, 2006. The study will be completed by June 20, 2008, and the supplement will be submitted by December 31, 2008.

2. To submit a supplement containing a final safety report and appropriate revised labeling describing the adverse event profile of Bevacizumab administered to patients with previously treated central nervous system (CNS) metastases. The supplement will contain information on an integrated safety population of least 50 patients with

previously treated CNS metastases enrolled on studies AVF3752g and AVF3671g to include the summary safety analyses, primary datasets with demographic, treatment and safety information, case report forms for all deaths and dropouts, narrative summaries for all patients with serious adverse events in either study. For those patients enrolled in study AVF3752g, the supplement will contain information on the number and size of brain metastases. Protocol AVF3752g was submitted to BB-IND 7023 on November 30, 2005. Protocol AVF3671 will be submitted by November 30, 2006, accrual of the minimum number of 50 patients will occur by January 31, 2008, and the supplement will be submitted by March 31, 2008.

3. To submit a safety update on an annual basis containing safety information summarizing and characterizing NCI-CTC version 3 Grade 2-5 adverse events involving the CNS from the following three placebo-controlled, randomized studies: OSI3364g (non-small cell lung cancer), AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). For studies which have not been completed, the annual safety update will be prepared by an independent, unblinded data coordinating center that will not share information with any individual involved in the design, conduct, and analysis of the trials. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005, and protocol AVF3693g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 30, 2006. Annual reports will be submitted by December 31, 2007, December 31, 2008, and December 31, 2009.

4. To submit a supplement containing a final safety report and revised labeling, if applicable, based on data from a minimum of 100 patients with CNS metastases (roughly half of whom were randomized to Bevacizumab plus additional anti-cancer agents) enrolled in studies OSI3364g, AVF3693g, and AVF3995g. The supplement will include summary analyses and primary datasets, including the number and size of CNS metastases for each patient. A statistical analysis plan for the integrated summary analyses will be submitted by June 30, 2007, and the supplement will be submitted by December 31, 2010.

5. To conduct a sub-study to address the impact of Bevacizumab on the QT interval. This sub-study will be added to three planned or ongoing randomized placebo-controlled studies in breast cancer, ovarian cancer, and extensive stage small cell lung cancer. The sub-study will collect replicate ECG measurements at baseline and at various time points correlating with drug exposure. Approximately 60 Bevacizumab-treated patients and 60 controls will be evaluated in this sub-study. A detailed protocol for this sub-study will be submitted by January 31, 2007. The sub-study will be initiated by June 30, 2007 and will be completed by June 30, 2010. A final study report and revised labeling, if applicable, will be submitted by December 31, 2010.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125085. Submit all study final reports to your BLA STN BL 125085. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm) for further information.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. The final printed labeling (FPL) must be identical to the enclosed labeling text dated October 11, 2006. Marketing product with FPL that is not identical to the approved labeling may render the product misbranded and an unapproved new drug. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please submit within 30 days content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text dated October 11, 2006. Upon receipt and

verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.
Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.
Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

This information will be included in your biologics license application file.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures: Revised Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125085/85

LABELING

10-11-06

1.14.2.3 Final Labeling Text

AVASTIN®
(Bevacizumab)

For Intravenous Use

WARNINGS

Gastrointestinal Perforations

AVASTIN administration can result in the development of gastrointestinal perforation, in some instances resulting in fatality. Gastrointestinal perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with AVASTIN (i.e., was not correlated to duration of exposure). The incidence of gastrointestinal perforation (gastrointestinal perforation, fistula formation, and/or intra-abdominal abscess) in patients with colorectal cancer and in patients with non-small cell lung cancer (NSCLC) receiving AVASTIN was 2.4% and 0.9%, respectively. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and vomiting. Gastrointestinal perforation should be included in the differential diagnosis of patients presenting with abdominal pain on AVASTIN. AVASTIN therapy should be permanently discontinued in patients with gastrointestinal perforation. (See **WARNINGS: Gastrointestinal Perforations** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

Wound Healing Complications

AVASTIN administration can result in the development of wound dehiscence, in some instances resulting in fatality. AVASTIN therapy should be permanently discontinued in patients with wound dehiscence requiring medical intervention. The appropriate interval between termination of AVASTIN and subsequent elective surgery required to avoid the risks of impaired wound healing/wound dehiscence has not been determined. (See **WARNINGS: Wound Healing Complications** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

Hemorrhage

Fatal pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and AVASTIN. The incidence of severe or fatal hemoptysis was 31% in patients with squamous histology and 2.3% in patients with NSCLC excluding predominant squamous histology. Patients with recent hemoptysis (≥1/2 tsp of red blood) should not receive AVASTIN. (See **WARNINGS: Hemorrhage, ADVERSE REACTIONS: Hemorrhage,** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

DESCRIPTION

AVASTIN® (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and has a molecular weight of approximately 149 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion. AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of Bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

Pharmacokinetics

The pharmacokinetic profile of Bevacizumab was assessed using an assay that measures total serum Bevacizumab concentrations (i.e., the assay did not distinguish between free Bevacizumab and Bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of AVASTIN weekly, every 2 weeks, or every 3 weeks, the estimated half-life of Bevacizumab was approximately 20 days (range 11–50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of Bevacizumab every 2 weeks was 2.8.

The clearance of Bevacizumab varied by body weight, by gender, and by tumor burden. After correcting for body weight, males had a higher Bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger V_c (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher Bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. In a randomized study of 813 patients (Study 1), there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with AVASTIN as compared to females and patients with low tumor burden. The relationship between Bevacizumab exposure and clinical outcomes has not been explored.

Special Populations

Analyses of demographic data suggest that no dose adjustments are necessary for age or sex.

Patients with renal impairment. No studies have been conducted to examine the pharmacokinetics of Bevacizumab in patients with renal impairment.

Patients with hepatic dysfunction. No studies have been conducted to examine the pharmacokinetics of Bevacizumab in patients with hepatic impairment.

CLINICAL STUDIES

AVASTIN® In Metastatic Colorectal Cancer (mCRC)

The safety and efficacy of AVASTIN in the treatment of patients with metastatic carcinoma of the colon or rectum were studied in three randomized, controlled clinical trials in combination with intravenous 5-fluorouracil–based chemotherapy. The activity of AVASTIN in patients with metastatic colorectal cancer that progressed on or after receiving both irinotecan based- and oxaliplatin based-chemotherapy regimens was evaluated in an open-access trial in combination with intravenous 5-fluorouracil-based chemotherapy.

AVASTIN in Combination with Bolus-IFL

Study 1 was a randomized, double-blind, active-controlled clinical trial evaluating AVASTIN as first-line treatment of metastatic carcinoma of the colon or rectum. Patients were randomized to bolus-IFL (irinotecan 125 mg/m^2 IV, 5-fluorouracil 500 mg/m^2 IV, and leucovorin 20 mg/m^2 IV given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus AVASTIN (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV plus AVASTIN (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, when the toxicity of AVASTIN in combination with the bolus-IFL regimen was deemed acceptable.

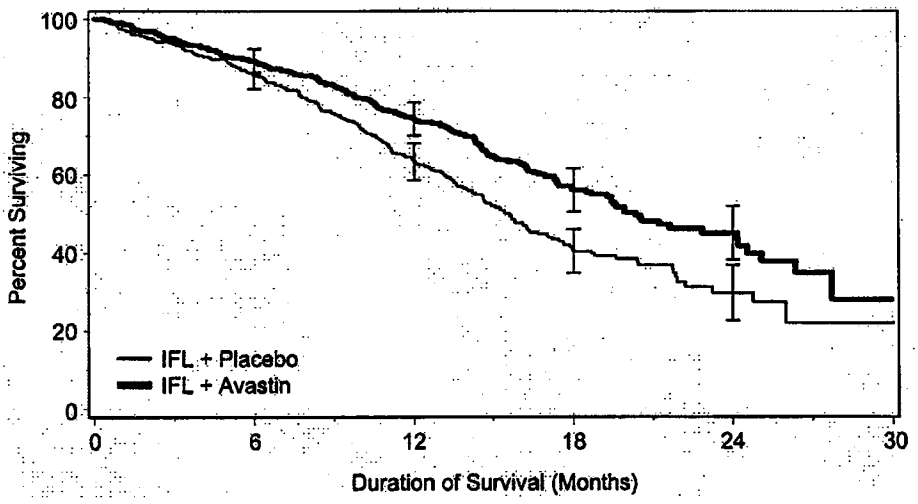
Of the 813 patients randomized to Arms 1 and 2, the median age was 60, 40% were female, and 79% were Caucasian. Fifty-seven percent had an ECOG performance status of 0. Twenty-one percent had a rectal primary and 28% received prior adjuvant chemotherapy. In the majority of patients, 56%, the dominant site of disease was extra-abdominal, while the liver was the dominant site in 38% of patients. Results are presented in Table 1 and Figure 1.

Table 1
Study 1 Efficacy Results

	IFL+Placebo	IFL+AVASTIN 5 mg/kg q 2 wks
Number of Patients	411	402
Overall Survival[a]		
Median (months)	15.6	20.3
Hazard ratio		0.66
Progression-free Survival[a]		
Median (months)	6.2	10.6
Hazard ratio		0.54
Overall Response Rate[b]		
Rate (percent)	35%	45%
Duration of Response		
Median (months)	7.1	10.4

[a] $p<0.001$ by stratified logrank test.
[b] $p<0.01$ by χ^2 test.

Figure 1
Duration of Survival in Study 1



Error bars represent 95% confidence intervals.

The clinical benefit of AVASTIN, as measured by survival in the two principal arms, was seen in the subgroups defined by age (<65 yrs, ≥65 yrs) and gender.

Among the 110 patients enrolled in Arm 3, median overall survival was 18.3 months, median progression-free survival was 8.8 months, overall response rate was 39%, and median duration of response was 8.5 months.

AVASTIN in Combination with 5-FU/LV Chemotherapy

Study 2 was a randomized, active-controlled clinical trial testing AVASTIN in combination with 5-FU/LV as first-line treatment of metastatic colorectal cancer. Patients were randomized to receive 5-FU/LV (5-fluorouracil 500 mg/m^2, leucovorin 500 mg/m^2 weekly for 6 weeks every 8 weeks) or 5-FU/LV plus AVASTIN (5 mg/kg every 2 weeks) or 5-FU/LV plus AVASTIN (10 mg/kg every 2 weeks). The primary endpoints of the trial were objective response rate and progression-free survival. Results are presented in Table 2.

Table 2
Study 2 Efficacy Results

	5-FU/LV	5-FU/LV+AVASTIN 5 mg/kg	5-FU/LV+AVASTIN 10 mg/kg
Number of Patients	36	35	33
Overall Survival			
Median (months)	13.6	17.7	15.2
Progression-free Survival			
Median (months)	5.2	9.0	7.2
Overall Response Rate			
Rate (percent)	17	40	24

Progression-free survival was significantly longer in patients receiving 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not receiving AVASTIN. However, overall survival and overall response rate were not significantly different. Outcomes for patients receiving 5-FU/LV

plus AVASTIN at 10 mg/kg were not significantly different than for patients who did not receive AVASTIN.

AVASTIN in Combination with 5-FU/LV and Oxaliplatin Chemotherapy

Study 3 was an open-label, randomized, 3-arm, active-controlled, multicenter clinical trial evaluating AVASTIN alone, AVASTIN in combination with 5-FU/LV and oxaliplatin (FOLFOX4), and FOLFOX4 alone in the second-line treatment of metastatic carcinoma of the colon or rectum. Patients were previously treated with irinotecan and 5-FU for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized to FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2 concurrently IV, then 5-FU 400 mg/m^2 IV bolus followed by 600 mg/m^2 continuously IV; Day 2: leucovorin 200 mg/m^2 IV, then 5-FU 400 mg/m^2 IV bolus followed by 600 mg/m^2 continuously IV; repeated every 2 weeks), FOLFOX4 plus AVASTIN, or AVASTIN monotherapy. AVASTIN was administered at a dose of 10 mg/kg every 2 weeks and for patients in the FOLFOX4 plus AVASTIN arm, prior to the FOLFOX4 chemotherapy on Day 1.

Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female, 87% were Caucasian, and 49% had an ECOG performance status of 0. Twenty-six percent had received prior radiation therapy, and 80% received prior adjuvant chemotherapy. Ninety-nine percent received prior irinotecan, with or without 5-FU for metastatic colorectal cancer, and 1% received prior irinotecan and 5-FU as adjuvant therapy.

The AVASTIN monotherapy arm of Study 3 was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee (DMC), based on evidence of decreased survival in the AVASTIN alone arm as compared to the FOLFOX4 alone arm. In the two remaining study arms, overall survival (OS) was significantly longer in patients receiving AVASTIN in

combination with FOLFOX4 as compared to those receiving FOLFOX4 alone (median OS 13.0 mos vs. 10.8 mos; hazard ratio 0.75 [95% CI 0.63, 0.89], p=0.001 stratified log rank test). In addition, patients treated with AVASTIN in combination with FOLFOX4 were reported to have significantly longer progression-free survival and a higher overall response rate based on investigator assessment. The clinical benefit of AVASTIN, as measured by survival, was seen in the subgroups defined by age (<65 yrs, ≥65 yrs) and gender.

AVASTIN in Third-Line Metastatic Colorectal Cancer

Study 4 was an open access, multicenter, single arm study that evaluated the activity of AVASTIN in combination with bolus or infusional 5-FU/LV in 339 patients with metastatic colorectal cancer with disease progression following both irinotecan- and oxaliplatin-containing chemotherapy regimens. The majority (73%) of patients received concurrent 5-FU/LV according to a bolus regimen.

There was one objective partial response in the first 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

AVASTIN® In Unresectable Non-Squamous, Non-Small Cell Lung Cancer (NSCLC)

The safety and efficacy of AVASTIN as first-line treatment of patients with locally advanced, metastatic, or recurrent non-squamous, NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study (Study 5, n=878), supported by a randomized, dose ranging, active controlled Phase 2 study (Study 6, n=98).

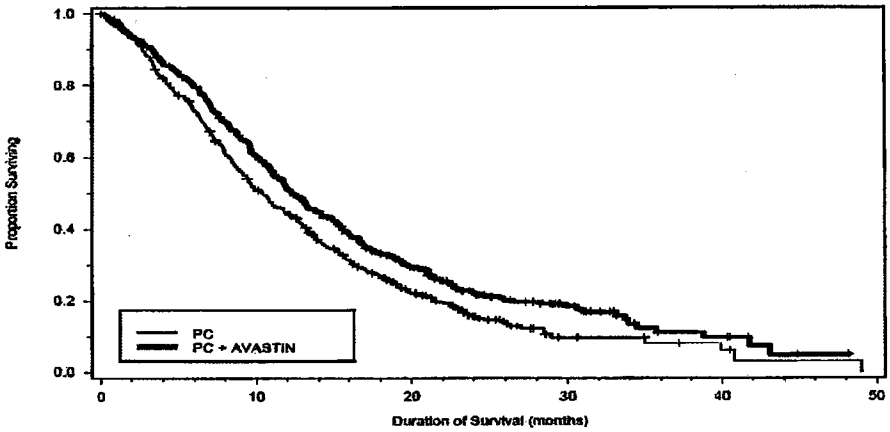
In Study 5, chemotherapy-naïve patients with locally advanced, metastatic or recurrent non-squamous NSCLC were randomized (1:1) to receive six cycles of paclitaxel 200 mg/m^2 and carboplatin AUC=6.0, both by IV infusion on day 1 (PC) or PC in combination with AVASTIN at a dose of 15 mg/kg by IV infusion on day 1 (PC plus AVASTIN). After completion or upon discontinuation of chemotherapy, patients in the PC plus

AVASTIN arm continued to receive AVASTIN alone until disease progression or until unacceptable toxicity. Cycles were repeated every 21 days. Patients with predominant squamous histology (mixed cell type tumors only), central nervous system (CNS) metastasis, gross hemoptysis (≥1/2 tsp of red blood), or unstable angina and those receiving therapeutic anticoagulation were excluded. The main outcome measure of the study was duration of survival.

Among the 878 patients randomized to the two treatment arms, the median age was 63, 46% were female, 43% were ≥ age 65, and 28% had ≥ 5% weight loss at study entry. Eleven percent had recurrent disease and of the remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease. The survival curves are presented in Figure 2. Overall survival was statistically significantly higher among patients receiving PC plus AVASTIN compared with those receiving PC alone; median OS was 12.3 mos vs. 10.3 mos (hazard ratio 0.80 [repeated 95% CI 0.68, 0.94], final p- value 0.013, stratified log-rank test). Based on investigator assessment which was not independently verified, patients were reported to have longer progression-free survival with AVASTIN in combination with PC compared to PC alone.

Figure 2

Duration of Survival in Study 5



In an exploratory analyses across patient subgroups, the impact of AVASTIN on overall survival was less robust in the following: women [HR = 0.99 (95% CI: 0.79, 1.25)], age ≥ 65 years [HR = 0.91 (95% CI: 0.72, 1.14)] and patients with ≥5% weight loss at study entry [HR = 0.96 (95% CI: 0.73, 1.26)].

INDICATIONS AND USAGE

AVASTIN®, in combination with intravenous 5-fluorouracil–based chemotherapy, is indicated for first-or second-line treatment of patients with metastatic carcinoma of the colon or rectum.

AVASTIN®, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.

CONTRAINDICATIONS

None.

WARNINGS

Gastrointestinal Perforations (See DOSAGE AND ADMINISTRATION: Dose Modifications)

Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation and in some instances with fatal outcome, occurs at an increased incidence in patients receiving AVASTIN as compared to controls. In Studies 1, 2, and 3, the incidence of gastrointestinal perforation (gastrointestinal perforation, fistula formation, and/or intra-abdominal abscess) in patients receiving AVASTIN was 2.4%. These episodes occurred with or without intra-abdominal abscesses and at various time points during treatment. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and emesis.

In post-marketing clinical studies and reports, gastrointestinal perforation, fistula and/or intra-abdominal abscess occurred in patients receiving AVASTIN for colorectal and for other types of cancer. The overall incidence in clinical studies was 1%, but may be higher in some cancer settings. Of the reported events, approximately 30% were fatal. Patients with gastrointestinal perforation, regardless of underlying cancer, typically present with abdominal pain, nausea and fever. Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of AVASTIN, with most events occurring within the first 50 days.

Permanently discontinue AVASTIN in patients with gastrointestinal perforation.

Wound Healing Complications (See DOSAGE AND ADMINISTRATION: Dose Modifications)

AVASTIN impairs wound healing in animal models. In clinical studies of AVASTIN, patients were not allowed to receive AVASTIN until at least 28 days had elapsed following surgery. In clinical studies of AVASTIN in combination with chemotherapy, there were 6 instances of dehiscence among 788 patients (0.8%).

The appropriate interval between discontinuation of AVASTIN and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined. In Study 1, 39 patients who received bolus-IFL plus AVASTIN underwent surgery following AVASTIN therapy; of these patients, six (15%) had wound healing/bleeding complications. In the same study, 25 patients in the bolus-IFL arm underwent surgery; of these patients, one of 25 (4%) had wound healing/bleeding complications. The longest interval between last dose of study drug and dehiscence was 56 days; this occurred in a patient on the bolus-IFL plus AVASTIN arm.

The interval between termination of AVASTIN and subsequent elective surgery should take into consideration the calculated half-life of AVASTIN (approximately 20 days).

Discontinue AVASTIN in patients with wound healing complications requiring medical intervention.

Hemorrhage (See DOSAGE AND ADMINISTRATION: Dose Modifications)

Two distinct patterns of bleeding have occurred in patients receiving AVASTIN. The first is minor hemorrhage, most commonly NCI-CTC Grade 1 epistaxis. The second is serious, and in some cases fatal, hemorrhagic events.

In Study 6, four of 13 (31%) AVASTIN-treated patients with squamous cell histology and two of 53 (4%) AVASTIN-treated patients with histology other than squamous cell, experienced serious or fatal pulmonary hemorrhage as compared to none of the 32 (0%) patients receiving chemotherapy alone. Of the patients experiencing pulmonary hemorrhage requiring medical intervention, many had cavitation and/or necrosis of the tumor, either pre-existing or developing during AVASTIN therapy. In Study 5, the rate of pulmonary hemorrhage requiring medical intervention for the PC plus AVASTIN arm was 2.3% (10 of 427)

compared to 0.5% (2 of 441) for the PC alone arm. There were seven deaths due to pulmonary hemorrhage reported by investigators in the PC plus AVASTIN arm as compared to one in the PC alone arm. Generally, these serious hemorrhagic events presented as major or massive hemoptysis without an antecedent history of minor hemoptysis during Avastin therapy. Do not administer AVASTIN to patients with recent history of hemoptysis of ≥1/2 tsp of red blood. Other serious bleeding events occurring in patients receiving AVASTIN across all indications include gastrointestinal hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke. Some of these events were fatal. (See **ADVERSE REACTIONS: Hemorrhage.**)

The risk of central nervous system (CNS) bleeding in patients with CNS metastases receiving AVASTIN has not been evaluated because these patients were excluded from late stage clinical studies following development of CNS hemorrhage in a patient with a CNS metastasis in a Phase 1 study.

Discontinue AVASTIN in patients with serious hemorrhage (i.e., requiring medical intervention) and initiate aggressive medical management. (See **ADVERSE REACTIONS: Hemorrhage.**)

Arterial Thromboembolic Events (see DOSAGE AND ADMINISTRATION: Dose Modifications and PRECAUTIONS: Geriatric Use)

Arterial thromboembolic events (ATE) occurred at a higher incidence in patients receiving AVASTIN in combination with chemotherapy as compared to those receiving chemotherapy alone. ATE included cerebral infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), angina, and a variety of other ATE. These events were fatal in some instances.

In a pooled analysis of randomized, controlled clinical trials involving

1745 patients, the incidence of ATE was 4.4% among patients treated with AVASTIN in combination with chemotherapy and 1.9% among patients receiving chemotherapy alone. Fatal outcomes for these events occurred in 7 of 963 patients (0.7%) who were treated with AVASTIN in combination with chemotherapy, compared to 3 of 782 patients (0.4%) who were treated with chemotherapy alone. The incidences of both cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial events (2.1% vs. 1.0%) were increased in patients receiving AVASTIN compared to chemotherapy alone. The relative risk of ATE was greater in patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%). (See **PRECAUTIONS: Geriatric Use.**)

The safety of resumption of AVASTIN therapy after resolution of an ATE has not been studied. Permanently discontinue AVASTIN in patients who experience a severe ATE during treatment. (See **DOSAGE AND ADMINISTRATION: Dose Modifications** and **PRECAUTIONS: Geriatric Use.)**

Hypertension (See DOSAGE AND ADMINISTRATION: Dose Modifications)

The incidence of severe hypertension was increased in patients receiving AVASTIN as compared to controls. Across clinical studies the incidence of NCI-CTC Grade 3 or 4 hypertension ranged from 8-18%.

Medication classes used for management of patients with NCI-CTC Grade 3 hypertension receiving AVASTIN included angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers. Development or worsening of hypertension can require hospitalization or require discontinuation of AVASTIN in up to 1.7% of patients. Hypertension can persist after discontinuation of AVASTIN. Complications can include hypertensive encephalopathy (in some cases fatal) and CNS hemorrhage.

In the post-marketing experience, acute increases in blood pressure associated with initial or subsequent infusions of AVASTIN have been reported (see **PRECAUTIONS: Infusion Reactions**). Some cases were serious and associated with clinical sequelae.

Permanently discontinue AVASTIN in patients with hypertensive crisis or hypertensive encephalopathy. Temporarily suspend AVASTIN in patients with severe hypertension that is not controlled with medical management. (See **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (See DOSAGE AND ADMINISTRATION: Dose Modifications)

RPLS has been reported in clinical studies (with an incidence of <0.1%) and in post-marketing experience. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present, but is not necessary for diagnosis of RPLS. Magnetic Resonance Imaging (MRI) is necessary to confirm the diagnosis of RPLS. The onset of symptoms has been reported to occur from 16 hours to 1 year after initiation of AVASTIN.

In patients developing RPLS, discontinue AVASTIN and initiate treatment of hypertension, if present. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating AVASTIN therapy in patients previously experiencing RPLS is not known.

Neutropenia and Infection (See PRECAUTIONS: Geriatric Use and ADVERSE REACTIONS: Neutropenia and Infection)

Increased rates of severe neutropenia, febrile neutropenia, and infection with severe neutropenia (including some fatalities) have been observed in patients treated with myelosuppressive chemotherapy plus AVASTIN. (See **PRECAUTIONS: Geriatric Use** and **ADVERSE REACTIONS: Neutropenia and Infection.**)

Proteinuria (See DOSAGE AND ADMINISTRATION: Dose Modifications)

The incidence and severity of proteinuria is increased in patients receiving AVASTIN as compared to control. In Studies 1, 3 and 5 the incidence of NCI-CTC Grade 3 and 4 proteinuria, characterized as >3.5 gm/24 hours, ranged up to 3.0% in AVASTIN-treated patients.

Nephrotic syndrome occurred in seven of 1459 (0.5%) patients receiving AVASTIN in clinical studies. One patient died and one required dialysis. In three patients, proteinuria decreased in severity several months after discontinuation of AVASTIN. No patient had normalization of urinary protein levels (by 24-hour urine) following discontinuation of AVASTIN.

The highest incidence of proteinuria was observed in a dose-ranging, placebo-controlled, randomized study of AVASTIN in patients with metastatic renal cell carcinoma, an indication for which AVASTIN is not approved, 24-hour urine collections were obtained in approximately half the patients enrolled. Among patients in whom 24-hour urine collections were obtained, four of 19 (21%) patients receiving AVASTIN at 10 mg/kg every two weeks, two of 14 (14%) patients receiving AVASTIN at 3 mg/kg every two weeks, and none of the 15 placebo patients experienced NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

Discontinue AVASTIN in patients with nephrotic syndrome. The safety of continued AVASTIN treatment in patients with moderate to severe proteinuria has not been evaluated. In most clinical studies, AVASTIN was interrupted for ≥2 grams of proteinuria/24 hours and resumed when proteinuria was <2 gm/24 hours. Patients with moderate to severe proteinuria based on 24-hour collections should be monitored regularly until improvement and/or resolution is observed. (See **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Congestive Heart Failure

Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left ventricular dysfunction, was reported in 25 of 1459 (1.7%) patients

receiving AVASTIN in clinical studies. The risk of CHF appears to be higher in patients receiving AVASTIN who have received prior or concurrent anthracyclines. In a controlled study in patients with breast cancer (an unlabelled indication), the incidence of CHF was higher in the AVASTIN plus chemotherapy arm as compared to the chemotherapy alone arm. Congestive heart failure occurred in 13 of 299 (4%) patients who received prior anthracyclines and/or left chest wall irradiation. Congestive heart failure occurred in six of 44 (14%) patients with relapsed acute leukemia (an unlabelled indication) receiving AVASTIN and concurrent anthracyclines in a single arm study.

The safety of continuation or resumption of AVASTIN in patients with cardiac dysfunction has not been studied.

PRECAUTIONS

General

Use AVASTIN with caution in patients with known hypersensitivity to AVASTIN or any component of this drug product.

Infusion Reactions

In clinical studies, infusion reactions with the first dose of AVASTIN were uncommon (<3%) and severe reactions occurred in 0.2% of patients. Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, NCI-CTC Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Adequate information on rechallenge is not available. AVASTIN infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with AVASTIN after experiencing a severe infusion reaction.

Surgery

AVASTIN therapy should not be initiated for at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of AVASTIN. Because of the potential for impaired wound healing, AVASTIN should be suspended prior to elective surgery. The appropriate interval between the last dose of AVASTIN and elective surgery is unknown; however, the half-life of AVASTIN is estimated to be 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and the interval chosen should take into consideration the half-life of the drug. (See **WARNINGS: Gastrointestinal Perforations** and **Wound Healing Complications.**)

Cardiovascular Disease

Patients were excluded from participation in AVASTIN clinical trials if, in the previous year, they had experienced clinically significant cardiovascular disease. In an exploratory analysis pooling the data from five randomized, placebo-controlled, clinical trials conducted in patients without a recent history of clinically significant cardiovascular disease, the overall incidence of arterial thromboembolic events, the incidence of fatal arterial thromboembolic events, and the incidence of cardiovascular thromboembolic events were increased in patients receiving AVASTIN plus chemotherapy as compared to chemotherapy alone.

Laboratory Tests

Blood pressure monitoring should be conducted every two to three weeks during treatment with AVASTIN. Patients who develop hypertension on AVASTIN may require blood pressure monitoring at more frequent intervals. Patients with AVASTIN-induced or -exacerbated hypertension who discontinue AVASTIN should continue to have their blood pressure monitored at regular intervals.

Patients receiving AVASTIN should be monitored for the development or worsening of proteinuria with serial urinalyses. Patients with a 2+ or greater urine dipstick reading should undergo further assessment, e.g., a

24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

Drug Interactions

No formal drug interaction studies with anti-neoplastic agents have been conducted. In Study 1, patients with colorectal cancer were given irinotecan/5-FU/leucovorin (bolus-IFL) with or without AVASTIN. Irinotecan concentrations were similar in patients receiving bolus-IFL alone and in combination with AVASTIN. The concentrations of SN38, the active metabolite of irinotecan, were on average 33% higher in patients receiving bolus-IFL in combination with AVASTIN when compared with bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus AVASTIN had a higher incidence of NCI-CTC Grade 3–4 diarrhea and neutropenia. Due to high inter-patient variability and limited sampling, the extent of the increase in SN38 levels in patients receiving concurrent irinotecan and AVASTIN is uncertain.

In Study 6, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with AVASTIN. However, 3 of the 8 patients receiving AVASTIN plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without AVASTIN had a greater paclitaxel exposure at Day 63 than at Day 0.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity data are available for AVASTIN in animals or humans.

AVASTIN may impair fertility. Dose-related decreases in ovarian and uterine weights, endometrial proliferation, number of menstrual cycles, and arrested follicular development or absent corpora lutea were observed in female cynomolgus monkeys treated with 10 or 50 mg/kg of AVASTIN for

Nursing Mothers

It is not known whether AVASTIN is secreted in human milk. Because human IgG1 is secreted into human milk, the potential for absorption and harm to the infant after ingestion is unknown. Women should be advised to discontinue nursing during treatment with AVASTIN and for a prolonged period following the use of AVASTIN, taking into account the half-life of the product, approximately 20 days [range 11–50 days]. (See **CLINICAL PHARMACOLOGY: Pharmacokinetics.**)

Pediatric Use

The safety and effectiveness of AVASTIN in pediatric patients has not been studied. However, physeal dysplasia was observed in juvenile cynomolgus monkeys with open growth plates treated for four weeks with doses that were less than the recommended human dose based on mg/kg and exposure. The incidence and severity of physeal dysplasia were dose-related and were at least partially reversible upon cessation of treatment.

Geriatric Use

In Study 1, NCI-CTC Grade 3–4 adverse events were collected in all patients receiving study drug (396 bolus-IFL plus placebo; 392 bolus-IFL plus AVASTIN; 109 5-FU/LV plus AVASTIN), while NCI-CTC Grade 1 and 2 adverse events were collected in a subset of 309 patients. There were insufficient numbers of patients 65 years and older in the subset in which NCI-CTC Grade 1-4 adverse events were collected to determine whether the overall adverse event profile was different in the elderly as compared to younger patients. Among the 392 patients receiving bolus-IFL plus AVASTIN, 126 were at least 65 years of age. Severe adverse events that occurred at a higher incidence (≥2%) in the elderly when compared to those less than 65 years were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of

AVASTIN on overall survival was similar in elderly patients as compared to younger patients.

In Study 3, patients age 65 and older receiving AVASTIN plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 5 patients age 65 and older receiving carboplatin, paclitaxel, and AVASTIN had a greater relative risk for proteinuria as compared to younger patients.

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients age 65 or older and 1127 patients less than 65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving AVASTIN with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%). (See **WARNINGS: Arterial Thromboembolic Events.**)

ADVERSE REACTIONS

The most serious adverse reactions in patients receiving AVASTIN were:

- Gastrointestinal Perforations (see **WARNINGS**)
- Wound Healing Complications (see **WARNINGS**)
- Hemorrhage (see **WARNINGS**)

- Arterial Thromboembolic Events (see **WARNINGS**)
- Hypertensive Crises (see **WARNINGS: Hypertension)**
- Reversible Posterior Leukoencephalopathy Syndrome (see **WARNINGS)**
- Neutropenia and Infection (see **WARNINGS**)
- Nephrotic Syndrome (see **WARNINGS: Proteinuria)**
- Congestive Heart Failure (see **WARNINGS**)

The most common adverse events in patients receiving AVASTIN were asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to AVASTIN in 1529 patients, including 665 receiving AVASTIN for at least 6 months and 199 receiving AVASTIN for at least one year. AVASTIN was studied primarily in placebo- and active-controlled trials (n = 501, and n = 1028, respectively).

Gastrointestinal Perforation

The incidence of gastrointestinal perforation across all studies ranged from 0-3.7%. The incidence of gastrointestinal perforation, in some cases fatal, in patients with mCRC receiving AVASTIN alone or in combination with chemotherapy was 2.4% compared to 0.3% in patients receiving only chemotherapy. The incidence of gastrointestinal perforation in NSCLC patients receiving AVASTIN was 0.9% compared to 0% in patients receiving only chemotherapy. (See **WARNINGS: Gastrointestinal**

Perforations and **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving AVASTIN as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus AVASTIN as compared to 4% (1/25) of patients who received bolus-IFL alone. In the same study, the incidence of wound dehiscence was also higher in the AVASTIN-treated patients (1% vs. 0.5%).

Hemorrhage

Severe or fatal hemorrhages, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in AVASTIN treated patients compared to patients treated with chemotherapy alone. NCI-CTC Grade 3-5 hemorrhagic events occurred in 4.7% of NSCLC patients and 5.2% of mCRC patients receiving AVASTIN compared to 1.1% and 0.7% for the control groups respectively. (See **WARNINGS: Hemorrhage.**)

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus AVASTIN compared with patients receiving bolus-IFL plus placebo. These events were generally mild in severity (NCI-CTC Grade 1) and resolved without medical intervention. Additional mild to moderate hemorrhagic events reported more frequently in patients receiving bolus-IFL plus AVASTIN when compared to those receiving bolus-IFL plus placebo included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). (See **WARNINGS: Hemorrhage** and **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Arterial Thromboembolic Events

The incidence of arterial thromboembolic events was increased in NSCLC patients receiving PC plus AVASTIN (3.0%) compared with patients receiving PC alone (1.4%). Five events were fatal in the PC plus AVASTIN arm, compared with 1 event in the PC alone arm. This increased risk is consistent with that observed in patients with mCRC. (See **WARNINGS: Arterial Thromboembolic Events, DOSAGE AND ADMINISTRATION: Dose Modifications,** and **PRECAUTIONS: Geriatric Use.**)

Venous Thromboembolic Events

The incidence of NCI-CTC Grade 3–4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving AVASTIN with chemotherapy as compared to those receiving chemotherapy alone. In addition, in patients with mCRC the risk of developing a second subsequent thromboembolic event in patients receiving AVASTIN and chemotherapy is increased compared to patients receiving chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus AVASTIN arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus AVASTIN and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of NCI-CTC Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus AVASTIN and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following NCI-CTC Grade 3 and 4 venous thromboembolic events was higher in patients receiving bolus-IFL plus AVASTIN as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

Hypertension

Fatal CNS hemorrhage complicating AVASTIN induced hypertension can occur.

In Study 1, the incidences of hypertension and of severe hypertension were increased in patients with mCRC receiving AVASTIN compared to those receiving chemotherapy alone (see Table 3).

Table 3
Incidence of Hypertension and Severe Hypertension in Study 1

	Arm 1 IFL+Placebo (n=394)	Arm 2 IFL+AVASTIN (n=392)	Arm 3 5-FU/LV+AVASTIN (n=109)
Hypertension[a] (>150/100 mmHg)	43%	60%	67%
Severe Hypertension[a] (>200/110 mmHg)	2%	7%	10%

[a] This includes patients with either a systolic or diastolic reading greater than the cutoff value on one or more occasions.

Among patients with severe hypertension in the AVASTIN arms, slightly over half the patients (51%) had a diastolic reading greater than 110 mmHg associated with a systolic reading less than 200 mmHg.

Similar results were seen in patients receiving AVASTIN alone or in combination with FOLFOX4 or carboplatin and paclitaxel. (See **WARNINGS: Hypertension** and **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Neutropenia and Infection

An increased incidence of neutropenia has been reported in patients receiving AVASTIN and chemotherapy compared to chemotherapy alone. In Study 1, the incidence of NCI-CTC Grade 3 or 4 neutropenia was increased in patients with mCRC receiving IFL+AVASTIN (21%) compared to patients receiving IFL alone (14%). In Study 5, the incidence

of NCI-CTC Grade 4 neutropenia was increased in patients with NSCLC receiving PC plus AVASTIN (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus AVASTIN vs. 1.8% for PC alone). There were 19 (4.5%) infections with NCI-CTC Grade 3 or 4 neutropenia in the PC plus AVASTIN arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus AVASTIN arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

Proteinuria

(See **WARNINGS: Proteinuria, DOSAGE AND ADMINISTRATION: Dose Modifications,** and **PRECAUTIONS: Geriatric Use.**)

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving AVASTIN has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with AVASTIN, primarily in combination with chemotherapy. High titer human anti-AVASTIN antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AVASTIN with the incidence of antibodies to other products may be misleading.

Metastatic Carcinoma of the Colon and Rectum

The data in Tables 4 and 5 were obtained in Study 1. All NCI-CTC Grade 3 and 4 adverse events and selected NCI-CTC Grade 1 and 2 adverse events (hypertension, proteinuria, thromboembolic events) were reported for the overall study population. The median age was 60, 60% were male, 79% were Caucasian, 78% had a colon primary lesion, 56% had extra-abdominal disease, 29% had prior adjuvant or neoadjuvant chemotherapy, and 57% had ECOG performance status of 0. The median duration of exposure to AVASTIN was 8 months in Arm 2 and 7 months in Arm 3. Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events, which occurred at a higher incidence (≥2%) in patients receiving bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are presented in Table 4.

Table 4
NCI-CTC Grade 3 and 4 Adverse Events in Study 1
(Occurring at Higher Incidence (≥2%) AVASTIN vs. Control)

	Arm 1 IFL+Placebo (n=396)	Arm 2 IFL+AVASTIN (n=392)
NCI-CTC Grade 3–4 Events	295 (74%)	340 (87%)
Body as a Whole		
Asthenia	28 (7%)	38 (10%)
Abdominal Pain	20 (5%)	32 (8%)
Pain	21 (5%)	30 (8%)
Cardiovascular		
Hypertension	10 (2%)	46 (12%)
Deep Vein Thrombosis	19 (5%)	34 (9%)
Intra-Abdominal Thrombosis	5 (1%)	13 (3%)
Syncope	4 (1%)	11 (3%)
Digestive		
Diarrhea	99 (25%)	133 (34%)
Constipation	9 (2%)	14 (4%)
Hemic/Lymphatic		
Leukopenia	122 (31%)	145 (37%)
Neutropenia[a]	41 (14%)	58 (21%)

[a] Central laboratories were collected on Days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

NCI-CTC Grade 1–4 adverse events which occurred at a higher incidence (≥5%) in patients receiving bolus-IFL plus AVASTIN as compared to the bolus-IFL plus placebo arm, are presented in Table 5.

Table 5
NCI-CTC Grade 1–4 Adverse Events in Study 1
(Occurring at Higher Incidence (≥5%) in IFL+AVASTIN vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+AVASTIN (n=102)	Arm 3 5-FU/LV+AVASTIN (n=109)
Body as a Whole			
Pain	54 (55%)	62 (61%)	67 (62%)
Abdominal Pain	54 (55%)	62 (61%)	55 (50%)
Headache	19 (19%)	27 (26%)	30 (26%)
Cardiovascular			
Hypertension	14 (14%)	23 (23%)	37 (34%)
Hypotension	7 (7%)	15 (15%)	8 (7%)
Deep Vein Thrombosis	3 (3%)	9 (9%)	6 (6%)
Digestive			
Vomiting	46 (47%)	53 (52%)	51 (47%)
Anorexia	29 (30%)	44 (43%)	38 (35%)
Constipation	28 (29%)	41 (40%)	32 (29%)
Stomatitis	18 (18%)	33 (32%)	33 (30%)
Dyspepsia	15 (15%)	25 (24%)	19 (17%)
GI Hemorrhage	6 (6%)	25 (24%)	21 (19%)
Weight Loss	10 (10%)	15 (15%)	18 (16%)
Dry Mouth	2 (2%)	7 (7%)	4 (4%)
Colitis	1 (1%)	6 (6%)	1 (1%)
Hemic/Lymphatic			
Thrombocytopenia	0	5 (5%)	5 (5%)
Nervous			
Dizziness	20 (20%)	27 (26%)	21 (19%)

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Table 5 (cont'd)
NCI-CTC Grade 1–4 Adverse Events in Study 1
(Occurring at Higher Incidence (≥5%) in IFL+AVASTIN vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+AVASTIN (n=102)	Arm 3 5-FU/LV+AVASTIN (n=109)
Respiratory			
Upper Respiratory Infection	38 (39%)	48 (47%)	44 (40%)
Epistaxis	10 (10%)	36 (35%)	35 (32%)
Dyspnea	15 (15%)	26 (26%)	27 (25%)
Voice Alteration	2 (2%)	9 (9%)	6 (6%)
Skin/Appendages			
Alopecia	25 (26%)	33 (32%)	6 (6%)
Skin Ulcer	1 (1%)	6 (6%)	7 (6%)
Special Senses			
Taste Disorder	9 (9%)	14 (14%)	23 (21%)
Urogenital			
Proteinuria	24 (24%)	37 (36%)	39 (36%)

The data in Table 6 were obtained in Study 3. Only NCI-CTC Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment were reported. The median age was a 61 years, 40% were female, 87% were Caucasian, 99% received prior chemotherapy for metastatic colorectal cancer, 26% had received prior radiation therapy, and the 49% had an ECOG performance status of 0. Selected NCI-CTC Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events which occurred at a higher incidence in patients receiving FOLFOX4 plus AVASTIN as compared to those who received FOLFOX4 alone, are presented in Table 6. These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 3.

Table 6
NCI-CTC Grade 3-5 Non-Hematologic and
Grade 4-5 Hematologic Adverse Events in Study 3
(Occurring at Higher Incidence (≥2%)
with AVASTIN+FOLFOX4 vs. FOLFOX4)

	FOLFOX4 (n=285)	FOLFOX4+ AVASTIN (n=287)	AVASTIN (n=234)
Patients with at least one event	171 (60%)	219 (76%)	87 (37%)
Gastrointestinal			
Diarrhea	36 (13%)	51 (18%)	5 (2%)
Nausea	13 (5%)	35 (12%)	14 (6%)
Vomiting	11 (4%)	32 (11%)	15 (6%)
Dehydration	14 (5%)	29 (10%)	15 (6%)
Ileus	4 (1%)	10 (4%)	11 (5%)
Neurology			
Neuropathy–sensory	26 (9%)	48 (17%)	2 (1%)
Neurologic–other	8 (3%)	15 (5%)	3 (1%)
Constitutional symptoms			
Fatigue	37 (13%)	56 (19%)	12 (5%)
Pain			
Abdominal pain	13 (5%)	24 (8%)	19 (8%)
Headache	0 (0%)	8 (3%)	4 (2%)
Cardiovascular (general)			
Hypertension	5 (2%)	26 (9%)	19 (8%)
Hemorrhage			
Hemorrhage	2 (1%)	15 (5%)	9 (4%)

Non-Squamous, Non-Small Cell Lung Cancer

The data in Table 7 were obtained in Study 5. Only NCI-CTC Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were reported. The median age was 63, 46% were female, no patients had received prior chemotherapy, 76% had Stage IV disease, 12% had Stage IIIB disease with malignant pleural effusion, 11% had recurrent disease, and 40% had an ECOG performance status of 0. The median duration of exposure to AVASTIN was 4.9 months.

NCI-CTC Grade 3, 4, and 5 adverse events that occurred at a ≥2% higher incidence in patients receiving PC plus AVASTIN as compared with PC alone are presented in Table 7.

Table 7
NCI-CTC Grade 3–5 Non-Hematologic and Grade 4 and 5 Hematologic Adverse Events in Study 5 (Occurring at a ≥2% Higher Incidence in AVASTIN-Treated Patients Compared with Control)

NCI-CTC Category Term[a]	No. (%) of NSCLC Patients	
	PC (n=441)	PC + AVASTIN (n=427)
Any event	286 (65%)	334 (78%)
Blood/bone marrow		
Neutropenia	76 (17%)	113 (27%)
Constitutional symptoms		
Fatigue	57 (13%)	67 (16%)
Cardiovascular (general)		
Hypertension	3 (0.7%)	33 (8%)
Vascular		
Venous thrombus/embolism	14 (3%)	23 (5%)
Infection/febrile neutropenia		
Infection without neutropenia	12 (3%)	30 (7%)
Infection with NCI-CTC Grade 3 or 4 neutropenia	9 (2%)	19 (4%)
Febrile neutropenia	8 (2%)	23 (5%)
Pulmonary/upper respiratory		
Pneumonitis/pulmonary infiltrates	11 (3%)	21 (5%)
Metabolic/laboratory		
Hyponatremia	5 (1%)	16 (4%)
Pain		
Headache	2 (0.5%)	13 (3%)
Renal/genitourinary		
Proteinuria	0 (0%)	13 (3%)

[a] Events were reported and graded according to NCI-CTC, Version 2.0. Per protocol, investigators were required to report NCI-CTC Grade 3–5 non-hematologic and Grade 4 and 5 hematologic events.

Other Serious Adverse Events

The following additional serious adverse events occurred in at least one subject treated with AVASTIN in clinical studies or post-marketing experience:

Body as a Whole: polyserositis

Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic ulceration

Hemic and lymphatic: pancytopenia

Respiratory: nasal septum perforation

OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

DOSAGE AND ADMINISTRATION

Do not initiate AVASTIN until at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of AVASTIN.

Metastatic Carcinoma of the Colon or Rectum

AVASTIN, used in combination with intravenous 5-FU-based chemotherapy, is administered as an intravenous infusion (5 mg/kg or 10 mg/kg) every 14 days.

The recommended dose of AVASTIN, when used in combination with bolus-IFL, is 5 mg/kg.

The recommended dose of AVASTIN, when used in combination with FOLFOX4, is 10 mg/kg.

Non-Squamous, Non-Small Cell Lung Cancer

The recommended dose of AVASTIN is 15 mg/kg, as an IV infusion every 3 weeks.

Dose Modifications

There are no recommended dose reductions for the use of AVASTIN. If needed, AVASTIN should be either discontinued or temporarily suspended as described below.

AVASTIN should be permanently discontinued in patients who develop gastrointestinal perforation, wound dehiscence requiring medical intervention, serious bleeding, a severe arterial thromboembolic event, nephrotic syndrome, hypertensive crisis or hypertensive encephalopathy. In patients developing RPLS, discontinue AVASTIN and initiate treatment of hypertension, if present. (See **WARNINGS: Reversible Posterior Leukoencephalopathy Syndrome.**)

Temporary suspension of AVASTIN is recommended in patients with evidence of moderate to severe proteinuria pending further evaluation and in patients with severe hypertension that is not controlled with medical management. The risk of continuation or temporary suspension of AVASTIN in patients with moderate to severe proteinuria is unknown.

AVASTIN should be suspended at least several weeks prior to elective surgery. (See **WARNINGS: Gastrointestinal Perforation** and **Wound Healing Complications** and **PRECAUTIONS: Surgery.**) AVASTIN should not be resumed until the surgical incision is fully healed.

Preparation for Administration

AVASTIN should be diluted for infusion by a healthcare professional using aseptic technique. Withdraw the necessary amount of AVASTIN to obtain the required dose and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Diluted AVASTIN solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for up to 8 hours. No incompatibilities between AVASTIN and polyvinylchloride or polyolefin bags have been observed.

AVASTIN infusions should not be administered or mixed with dextrose solutions.

Administration

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. The initial AVASTIN dose should be delivered over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Stability and Storage

AVASTIN vials must be refrigerated at 2–8°C (36–46°F). AVASTIN vials should be protected from light. Store in the original carton until time of use. **DO NOT FREEZE. DO NOT SHAKE.**

HOW SUPPLIED

AVASTIN is supplied as 4 mL and 16 mL of a sterile solution in single-use glass vials to deliver 100 and 400 mg of Bevacizumab per vial, respectively.

Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN (25 mg/mL). NDC 50242-060-01

Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN (25 mg/mL). NDC 50242-061-01

REFERENCES

1. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997;57:4593-9.

AVASTIN®
(Bevacizumab)
For Intravenous Use

Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

7455309
LV0017
4835701
Initial U.S.Approval: February 2004
Code Revision Date: October 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125085/85

MEDICAL REVIEW(S)

TERTIARY REVIEW
BL STN 125085.85

FROM: Patricia Keegan, M.D., Director Patricia Keegan 10/11/2006
Division of Biologic Oncology Products/OODP/CDER/OND

SUBJECT: Recommendation for Approval Action on BL STN 125085.85

TO: BL STN 125085.85

Recommendation:
I concur with the recommendations of the medical officer and statistician that this supplement be approved with the final labeling provided by Genentech on October 11, 2006, incorporating changes supported by BL STN125085.85. The approval is based on the demonstration of a clinically significant and highly statistically significant prolongation of overall survival when Avastin® 15 mg/kg is administered intravenously every three weeks with carboplatin/paclitaxel chemotherapy for 6 cycles then every three weeks thereafter until disease progression as initial systemic therapy of patients with unresectable, non-squamous, non-small cell lung cancer. The risks of Avastin® are well-established, can be minimized through appropriate patient selection, and while serious and sometimes fatal, did not outweigh the benefits of prolongation of time to death.

Introduction:
Avastin® (bevacizumab) was approved by the U.S. Food and Drug Administration (FDA) on February 26, 2004 for use in combination with intravenous (IV) 5-fluorouracil (5-FU)-based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon and rectum. Avastin® is a humanized IgG1 monoclonal antibody that binds to vascular endothelial growth factor and competitively inhibits the binding of VEGF to its receptor (VEGFr). This results in inhibition of VEGF activity in both *in vitro* and *in vivo* assay systems. The mechanism(s) through which bevacizumab mediates anti-tumor activity is unknown, buf is postulated to include inhibition of tumor vasculature formation and increased tumor vascular permeability leading to increased local chemotherapeutic drug delivery.

The original approval of Avastin® was based upon the results of a single, placebo-controlled, multicenter trial (Protocol AVF 2107g). The primary comparison was between two study arms comprised of 813 patients. The study demonstrated that the addition of Avastin® to irinotecan, 5-FU, and leucovorin (IFL) chemotherapy resulted in a highly statistically significant prolongation of overall survival (median survival 20.3 m vs. 15.6 m, $p < 0.001$, stratified log-rank test) and consistent effects on progression-free survival (median PFS 10.6 m vs. 6.2 m, $p<0.001$), overall response rate (45% vs. 35%, $p<0.01$ χ^2 test), and response duration (median 10.4 m vs. 7.1 m).

The current application is supported by the results of a single, open-label, randomized (1:1), active-control trial (E4599). The primary efficacy study was conducted by the

Eastern Cooperative Oncology Group (ECOG) in 878 patients with unresectable non-squamous, non-small cell lung cancer who had not received prior systemic therapy. The study demonstrated a statistically significant improvement in overall survival for patients receiving bevacizumab in combination with carboplatin/ paclitaxel (BV/CP) as compared to those receiving chemotherapy alone (CP). Secondary endpoints included overall response rate (ORR), response duration, and progression-free survival (PFS) as determined by study investigators.

In addition, Genentech submitted the results of a three-arm, 99-patient, dose-ranging, active-controlled Phase 2 study of CP alone or in combination with bevacizumab at a dose of 15 mg/kg every three weeks or in combination with bevacizumab at a dose of 7.5 mg/kg every three weeks. This study served as the basis for the dose and schedule used in the Phase 3 study (E4599). The primary endpoint of the Phase 2 study (AVF0757g) was progression-free survival; results were presented both for investigator- and an external-review committee determination of tumor-related endpoints. Both progression-free survival and overall response rates were higher among patients receiving CP plus 15 mg/kg of bevacizumab as compared to those receiving only chemotherapy. There was no evidence of benefit for those receiving the intermediate (7.5 mg/kg) dose of bevacizumab plus chemotherapy as compared to chemotherapy alone when results were based on the masked, independent determination of PFS and ORR.

Regulatory history

The primary study (Protocol E4599) supporting this efficacy supplement was conducted by ECOG under an NCI-sponsored IND for bevacizumab. Neither the NCI, ECOG, nor Genentech requested an end-of-Phase 2 meeting with the FDA to discuss the adequacy of the trial design to support a labeling expansion. The first patient was enrolled on August 22, 2001 and the last patient was enrolled on April 8, 2004. The study was amended seven times during the conduct of the study but prior to the first efficacy analysis; two additional amendments occurred after the final analysis, providing additional information on bevacizumab treatment in the limited number of patients remaining on therapy.

A summary of interactions between FDA, NCI, and Genentech on this file include:

- May 14, 2001: Protocol E4599 was submitted to IND 7921 (the NCI-sponsored IND for bevacizumab)
- June 5, 2003: FDA issued a letter to NCI regarding suitability of the study to support labeling expansion, based upon Genentech's statements to FDA of their interest in the study. FDA requested additional information regarding the proposed analytic plan and the need to collect additional safety information.
- July 29, 2004: a formal statistical analysis plan was submitted
- Sept. 2, 2004: FDA held a meeting with Genentech to discuss the statistical analysis plan; Genentech was informed during the meeting that due to lack of blinding, of auditing to verify results, and of an external review committee to verify subjective endpoint results, the secondary endpoints based on tumor measurements could not be included in labeling.

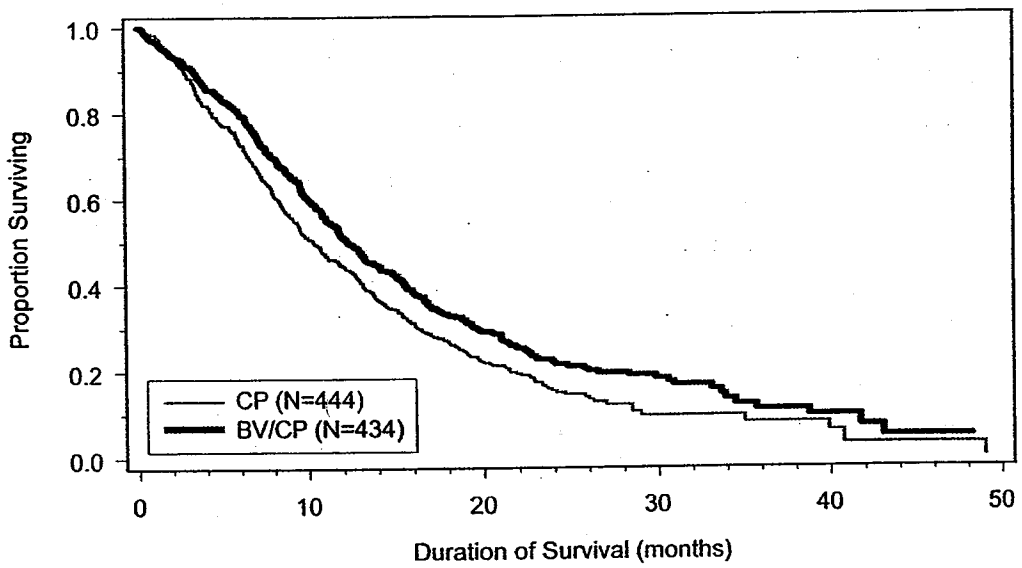
- Sept. 16, 2004: FDA held a meeting with the NCI regarding data auditing for verification of efficacy data. NCI noted that auditing of a specified study was not the goal of the process.
- Oct. 8, 2004: Genentech submitted a revised statistical analysis plan
- Nov. 2, 2004: the first interim analysis was conducted by the ECOG data monitoring committee (DMC)
- March 9, 2005: a second interim [and final] analysis was conducted by the ECOG DMC, utilizing a data cut-off of Feb. 9, 2005. The analysis results crossed the pre-specified boundary for statistical significance.
- July 21, 2005: FDA held a pre-BLA meeting with Genentech
- April 11, 2006: The efficacy supplement (BL STN 125085.85) was submitted to FDA

Efficacy results (See Dr. Jeff Summers' and Dr. Yuan-Li Shen's reviews)

Efficacy data are derived from E4599, a single, multicenter, randomized, open-label, active-controlled trial that enrolled 878 patients receiving initial systemic treatment for unresectable (recurrent, metastatic or locally advanced) non-squamous, non-small cell lung cancer. Patients were randomized 1:1 to an acceptable, standard chemotherapy regimen (paclitaxel and carboplatin for 6 cycles) or to the same chemotherapy regimen with the addition of bevacizumab at a dose of 15 mg/kg every three weeks. Bevacizumab was administered until disease progression.

The study results demonstrated a significant improvement and clinically important improvement in overall survival (median PFS 12.3 vs. 10.3 months, p=0.013) at ECOG's second planned interim analysis. Of note, the ECOG DMC followed the protocol's original plan for data analysis rather than the agreed-upon primary efficacy analyses in the statistical analysis plan submitted by Genentech. Thus, the ECOG DMC's analysis and decision to halt the study was based on an analysis of overall survival in the "eligible" population of 855 patients rather than the 878 patients in the ITT population identified in Genentech's analysis plan and as requested by FDA. In addition, there were 112 deaths that occurred prior to the data cut-off date of Feb. 9, 2005 specified for the second interim analysis that were not included in either the ECOG DMC's primary analysis of survival in the "eligible" population or the ECOG DMC's exploratory analysis of survival in the ITT population. Given the differences between ECOG's analysis and that described in Genentech's statistical analysis plan as well as the failure to include all events occurring prior to the data cut-off point for the second interim analysis, the use of the ECOG DMC's analysis in support of labeling claims was deemed inappropriate. As an alternative, the FDA statistician utilized the datasets and the final analytic plan of Oct 8, 2004 to arrive at the significance level that was acceptable for use in labeling claims. This analysis of overall survival was conducted in the ITT population (878 patients), included all events occurring prior to ECOG's pre-specified Feb. 9, 2005 data cut-off (581 deaths), and included an adjustment for the first interim analysis. Based on this analysis by FDA, the final p-value is 0.0134. For descriptive purposes, FDA performed analyses of overall survival in the ITT population (n=878) using the most

recent survival information; in this analysis, there are 698 events. The results of the overall survival based on the Dec. 30, 2005 cut-off are presented in the figure and table below:



	CP (n=444)	BV/CP (n=434)
Subjects who died	363	335
Subjects alive	81 (18.2%)	99 (22.8%)
Duration of survival (mo)		
Median	10.3	12.3
95% CI	(9.36, 11.73)	(11.30, 13.73)
Stratified analysis		
Hazard Ratio	0.80	
95% CI	(0.68, 0.94)	
p-value (log-rank)	0.013*	

* p-value derived from ITT analysis with 581 deaths

In standard exploratory subgroup analyses performed by FDA, the effects on overall survival differed by gender (HR 0.99 in women [n=400] vs. HR 0.69 in men [n=478]) and by age (HR 072 in patients <65 years [n=499] vs. 0.91 in patients ≥ 65 years [n=379]), however effects were similar in whites vs. non-whites. There is no plausible biologic rationale for lack of efficacy on the basis of either gender or age and these findings are not consistent with the subgroup analyses of overall survival by gender and age in the randomized, controlled trial in 813 patients with metastatic colorectal cancer. In order to further assess the efficacy of Avastin in these subgroups, at FDA's request, Genentech has agreed to submit the mature results of an ongoing Phase 3 trial in Europe

assessing the efficacy of the addition of Avastin to other chemotherapeutic regimens for the treatment of non-squamous, non-small cell lung cancer.

Analyses of progression-free survival, overall response rates, and response duration were conducted by ECOG and provided by Genentech, based upon investigator-assessment of tumor status. These analyses are confounded the open-label nature of the trial and differential assessments for tumor status between study arms after the completion of chemotherapy. FDA's concerns regarding these subjective endpoints were provided to both Genentech and NCI prior to conclusion of the trial; Genentech was advised of the potential consequences of failing to evaluate and confirm the findings by an independent evaluation committee masked to treatment assignment with regards to use in product labeling and promotional claims. The impact of bias cannot be readily assessed in open-label studies. However, the differences in subjective outcomes in the Phase 2 study (AVF0757g) indicate that such biases exist and should be considered in quantitative data presentation, as evidenced by both the magnitude and the direction of the differences between investigator- and independent reviewer-assessment of overall response rate (ORR) and time-to-progression (TTP) in the AVF 0757g trial displayed in the table, reproduced below from the supplement.

Table 2

Updated Results of Randomized Phase II Trial of Bevacizumab in Advanced NSCLC

	Group:	Control:	7.5 mg/kg:	15 mg/kg:	p-value:
ORR:	Investigator	18.8%	28.1%	31.4%	NS
	Independent Review Board	25%	21.9%	34.2%	NS
TTP:	Investigator	18.4 wk	18.7 wk	32.1 wk	0.023 (v. ctrl) 0.043 (v. 7.5)
	Independent Review Board	25.8 wk	17.7 wk	29.6 wk	0.32 (v. ctrl) 0.44 (v. 7.5)
MST:	All	56.8 wk	49.9 wk[1]	61.5 wk	NS

During the course of the review, these concerns were again discussed with Genentech, who conducted an evaluation of secondary endpoints based on tumor assessment in a randomly selected subset of patients enrolled in E4599. The results of this data verification exercise were submitted too late in the review to permit adequate assessment and, at Genentech's request, a description of the secondary endpoints in product labeling was limited to qualitative rather than quantitative findings. Using the investigators' assessments for progression-free survival and overall response rates, as well as in a series of exploratory analyses, the progression-free survival was prolonged among patients in

the BV/PC arm and the overall response rates were higher. Further description is provided in Dr. Summers' review

Safety (See Dr. Jeff Summers' review)

No new safety signals were identified in this study. The data collected in this study were limited, such that comparative toxicity could be evaluated only for severe and serious adverse events. Based on the review of the safety data, no new safety signals other than hyponatremia were identified. Treatment-related serious and life-threatening adverse events that are included in current labeling and were also identified to occur at a higher incidence in the Avastin-containing arm of E4599 include: hemorrhage, arterial-thromboembolic events, venous thromboembolic events, gastrointestinal perforation, hypertension, proteinuria, neutropenia, and infection (with or without concurrent neutropenia). Data collection for targeted adverse events, notably proteinuria, did not appear to have been conducted in accordance with the protocol, limiting characterization of this event.

Due to the protocol design, inadequate data were collected to characterize the safety and tolerability of this regimen, which involves higher dosing at less frequent intervals that the current labeling. In particular, data regarding the incidence of, and reason for, Avastin dose modification were not collected nor were data regarding the toxicities leading to treatment discontinuation collected. In comparison to previous studies, the incidence of serious adverse events did not appear to be markedly increased, suggesting that this new regimen is tolerable.

Given concerns regarding the use of Avastin in a patient population in which the incidence of CNS metastases is high (as compared with colorectal cancer), the FDA requested that, and Genentech agreed to, conduct studies and provide safety data in controlled clinical trials, focusing on the subset of patients who are document to have CNS metastases. The intent of these post-marketing commitments (PMC) is to further characterize the risks of CNS hemorrhage in such patients in a more efficient manner than can be accomplished through post-marketing surveillance, leading to more informative and rapid labeling changes, as needed, to accurately describe the risks.

Clinical Pharmacology (See Dr. Hong Zhao's review)

No samples were obtained in Study E4599 to characterize the pharmacokinetic profile of Avastin, carboplatin, or paclitaxel. Studies submitted in the original application have not identified important pharmacokinetic differences as a result of schedule (weekly vs. every 14 or every 21 days) other than peak serum levels. Pharmacokinetic data collected in the Phase 2 study (AVF0757g) suggested that there is decreased exposure to paclitaxel at day 63 among some patients receiving paclitaxel and carboplatin with bevacizumab as compared to those receiving chemotherapy alone. These findings are now included in product labeling (PRECAUTIONS: Drug-Drug Interactions).

DDMAC (See Carole Broadnax's review)

With one exception, all Ms. Broadnax's comments were included in FDA's revisions to the proposed labeling. The clinical team's reasoning for permitting the term "unresectable" was discussed at labeling meetings.

Post-marketing commitments:

Genentech has agreed, at FDA's request, to conduct the following post-marketing commitments in the following areas:

- Provide the results of an ongoing Phase 3 trial in NSCLC being conducted by Roche to further evaluate the effect of Avastin in women and in elderly patients
- Submit safety data from multiple studies and conduct integrated analyses to characterize the risks of CNS hemorrhage in patients with underlying CNS metastases.
- Conduct a substudy to characterize the impact of Avastin therapy on the corrected QT interval.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation 6
Division of Therapeutic Biologic Oncology Products

CLINICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125985.85
Drug Name:	Avastin/bevacizumab
Indication(s):	Non-Small Cell Lung Cancer
Applicant:	Genentech
Date(s):	Review Completed October 11, 2006.
Review Priority:	Priority
Medical Division:	Division of Biological Oncology Products (HFD-107)
Clinical Reviewer	Jeff Summers, M.D.
Clinical Team:	Jeff Summers, M.D.; Joe Gootenberg, M.D.; Patricia Keegan, M.D.
Project Manager:	Sharon Sickafuse
Biometrics Division:	Biologics and Therapeutics Statistical Staff (HFD-711)
Statistical Reviewer:	Yuan-Li Shen, Ph.D, Statistical Reviewer
Concurring Reviewers:	Mark Rothmann, Ph.D, Statistical Team Leader; Aloka, Chakravarty, Ph.D., Director

CLINICAL REVIEW

Application Type	BLAs
Submission Number	125085.85
Submission Code	
Letter Date	
Stamp Date	
PDUFA Goal Date	October 12, 2006
Reviewer Name	Jeff Summers
Review Completion Date	October 11, 2006
Established Name	Avastin/Bevacizumab
(Proposed) Trade Name	Avastin
Therapeutic Class	TBP Antiangiogenic
Applicant	Genentech
Priority Designation	P
Formulation	Intravenous
Dosing Regimen	15 μg/kg q 3 weeks
Indication	Non-Small Cell Lung Cancer
Intended Population	NSCLC (non-squamous)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is the recommendation of this reviewer to approve the BLA efficacy supplement STN 125085.85 for the use of Avastin at the recommended dose combined with carboplatin and paclitaxel as first line treatment to prolong survival in patients with unresectable or metastatic, non-squamous histology, NSCLC. Modifications, as contained herein, to the Applicant proposed label are required.

1.2 Recommendation on Postmarketing Actions

1.2.3 Other Phase 4 Requests

It is recommended that the Sponsor agree to the following PMCs:

1. To submit an efficacy supplement containing the final study report, including summary analyses, primary datasets and appropriate revised labeling describing the effects of overall survival in the entire population and by gender and age, from the Hoffman-LaRoche-sponsored study, BO17704, "A Randomized, Double-Blind, Multicenter Phase 3 Study of Bevacizumab in Combination with Cisplatin and Gemcitabine Versus Placebo, Cisplatin and Gemcitabine in Patients with Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer Who Have Not Received Prior Chemotherapy". A copy of the protocol was submitted to BB-IND 7023 on February 13, 2006 and patient accrual was completed by August 31, 2006. The study will be completed by June 20, 2008, and the supplement containing the final study report and revised labeling will be submitted by December 31, 2008.
2. To submit as a supplement a final safety report, and revised labeling, describing the adverse event profile of Avastin administered to patients with previously treated central nervous system (CNS) metastases. The supplement will contain information on an integrated safety population of at least 50 patients with previously treated CNS metastases enrolled on studies AVF3752g or AVF3671g, to include summary safety analyses, primary datasets with demographic, treatment and safety information, case report forms for all deaths and dropouts, and narrative summaries for all patients with serious adverse events in either study. For those patients enrolled in Study AVF3752g, the supplement will contain information on the number and size of brain metastases. Protocol AVF3752g was submitted to BB-IND 7023 on November 30, 2005. Protocol AVF3671g will be submitted by November 30, 2006, accrual of the minimum number of 50 patients will occur by January 31, 2008 and the supplement containing the final safety report and revised labeling will be submitted by March 31, 2008.
3. To submit a safety update on an annual basis containing safety information summarizing and characterizing NCI CTC ver. 3 Grade 2-5 adverse events involving the CNS from the following three placebo-controlled, randomized studies: OSI3364g (non-small cell lung

cancer) and AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). For studies which have not been completed, the annual update of information will be generated by an independent unblinded data coordinating center that will not share information with any individual involved in the design, conduct or analysis of the trials. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005 and protocol AVF3995g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 30, 2006, and the annual safety updates will be submitted by Dec. 31, 2007, Dec. 31, 2008, and Dec, 31, 2009.

4. To submit as a supplement a final safety report containing revised labeling, as applicable, based on data from a minimum of 100 patients with CNS metastases (roughly half of whom were randomized to Bevacizumab plus additional anti-cancer agents) enrolled in studies OSI3364g (non-small cell lung cancer), AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). The supplement will include summary analyses and primary datasets, including the number and size of CNS metastases for each patient. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005 and protocol AVF3993g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 20, 2006, a statistical analysis plan for integrated summary analyses will be submitted by June 30, 2007, and the supplement containing the final safety report and revised labeling will be submitted by December 31, 2010.

5. To conduct a sub-study to address the impact of Bevacizumab on the QT interval. This sub-study will be added to three planned or ongoing randomized placebo-controlled studies in breast cancer, ovarian cancer, and extensive stage small cell lung cancer. The sub-study will collect replicate ECG measurements at baseline and at various time points correlating with drug exposure. Approximately 60 Bevacizumab-treated patients and 60 controls will be evaluated in this sub-study. A detailed protocol for this sub-study will be submitted by January 31, 2007. The sub-study will be initiated by June 30, 2007 and will be completed by June 30, 2010. A report based on this study will be submitted by December 31, 2010.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical program leading to this submission consisted of two studies testing carboplatin/paclitaxel (CP) with and without bevacizumab in previously untreated patients with advanced or metastatic NSCLC. A small Genentech sponsored study (AVF0757g) that compared two dose levels of bevacizumab with carboplatin/paclitaxel (BV/CP) compared to CP alone in 99 subjects suggested a longer time to disease progression in the 15 mg/kg every 3 weeks bevacizumab + CP treatment arm. Study AVF0757g also identified squamous histology as a risk factor for life-threatening hemoptysis. A larger open-label, controlled, randomized study to evaluate the efficacy and safety of BV/CP versus CP in patients with either recurrent or previously untreated, unresectable, or metastatic non-squamous histology NSCLC was conducted by the Eastern Cooperative Oncology Group (ECOG). The study accrued 878 subjects, randomized 1:1, over approximately 3 years duration. Patients received CP or BV/CP (bevacizumab 15 mg/kg intravenous) every three weeks for 6 cycles. Patients on the BV/CP arm

continued on bevacizumab until disease progression or unacceptable toxicity. The primary outcome measurement of the study was duration of survival. The ECOG DMC determined during the March 2005 second interim analysis (data cutoff date February 2005) that the survival endpoint had met the prespecified criterion for statistical significance. The final descriptive analyses, as provided in this submission, were based on 698 events with a data cutoff date of December 30, 2005. The inferential values stated in this review were determined from the March 2005 second interim analysis with the inclusion of 112 events (death) that were not originally included in the Sponsor's and Applicant's analysis but that occurred prior to the February 2005 data cutoff date.

1.3.2 Efficacy

The primary efficacy outcome measure for this study was the duration of survival. The analysis was based on an ITT population. Stratified analysis of the primary endpoint of duration of survival for all randomized patients demonstrated a statistically significant increase in the duration of survival among patients in the carboplatin and paclitaxel + bevacizumab arm compared with those in the carboplatin and paclitaxel arm (nominal p-value = 0.012). Median survival was 12.3 months in the BV/CP arm and 10.3 months in the CP arm.

The secondary endpoints of PFS and objective response were compromised by the open label design of the study, the lack of an independent radiology review charter, and the lack of a blinded centralized review of the tumor imaging radiology assessments. Although ECOG utilized a "centralized review process" this consisted of a review of the primary site measurements and did not involve blinded review of tumor assessment imaging studies.

Stratified analysis of PFS for all randomized patients demonstrated a statistically significant increase in PFS in patients in the BV/CP arm compared with patients in the CP arm ($p < 0.0001$). Median PFS was 6.4 months in the BV/CP arm compared with 4.8 months in the CP arm. A similar proportion (21%) of subjects were censored in each treatment arm in the Sponsor provided PFS analysis. Subjects were censored at the time of last tumor assessment if study treatment was discontinued for toxicity reasons or for administration of non-protocol anti-tumor therapy prior to disease progression. The two treatment arms had different frequencies of tumor assessments, as mandated by the protocol, after cycle 6 was completed. A landmark analysis of PFS at week 19 demonstrated a PFS rate of 68.5% in the BV/CP arm compared with 54.1% in the CP arm ($p < 0.0001$). The frequency of tumor assessment was every 9 weeks in the BV/CP arm and every 3 months in the CP arm after cycle 6 was completed. If an ascertainment bias existed it would have favored the CP treatment arm and therefore the CP treatment arm PFS interval is possibly an over representation of the true interval.

The objective response rate in randomized patients with measurable disease (approximately 91% of subjects in each treatment arm) was significantly higher ($p < 0.0001$) in the BV/CP arm (29.0%) than in the CP arm (12.9%). The majority of objective responses reported were partial responses (PRs) with only1.3% complete responses (CRs) in the BV/CP arm and 0.5% complete responses in the CP arm. The determination of duration of objective response was based on a non-randomized subset of patients and formal hypothesis testing was not performed. A descriptive comparison of treatment arms reveals a 6.2 months duration of response in the BV/CP arm and 5.0 months duration of response in the CP arm.

1.3.3 Safety

Although the safety data for study E4599 was limited by the protocol mandated collection mechanisms, no new serious adverse event safety signal was identified from the data. The clinical safety component of the study was conducted such that all grade 3-5 non-hematologic and grade 4-5 hematologic adverse events were captured on the ECOG case report forms. The onset dates and end dates of adverse events were not collected on the Toxicity CRF and instead a variable reporting period ranging from 1-392 days (median 21) in duration was recorded. Adverse events that led to the discontinuation of bevacizumab were not collected during the conduct of the study. No attempt at retrospective identification of the adverse events responsible for discontinuation of bevacizumab was made. In addition to the E4599 Adverse Event case report form, selective toxicity data was collected through the AdEEERs expedited reporting system for the BV/CP arm. AdEERS reporting requirements changed over time during the conduct of the study. Expedited adverse events for the CP arm were collected through the MedWatch reporting system. The MedWatch data for the CP arm is not provided for review in this supplement.

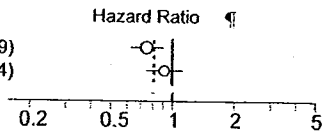
1.3.4 Dosing Regimen and Administration

The Avastin Package Insert recommended dose is 5 to 10 mg/kg administered IV every two weeks. The E4599 study submitted employed a dose of 15 mg/kg administered every three weeks.

1.3.6 Special Populations

Elderly Subjects ≥ 65 years of age (379 subjects) exhibited a decreased treatment effect from the addition of bevacizumab to carboplatin and paclitaxel in prolonging the duration of survival as those subjects less than 65 years of age. There was an eight fold greater treatment effect from bevacizumab in patients less than 65 years of age compared to subjects over 65 years of age as can be seen below.

Baseline Characteristic	Total n	CP (n=444) Median n (months)	BV/CP (n=434) Median n (months)	Hazard Ratio (95% CI)
40–64	486	246 9.8	240 13.1	0.73 (0.60 - 0.89)
≥ 65	379	194 11.7	185 11.3	0.91 (0.72 - 1.14)



No notable increase in the relative risk for specific adverse events was evident in the study population greater than 65 years of age, although the study data suggested possible increased relative risk for proteinuria and leukopenia.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF).

Neutralization of the biologic activity of VEGF can result in the reduction of tumor vascularization and subsequent tumor growth. Bevacizumab was approved by the U.S. Food and Drug Administration (FDA) in February 2004 for use in combination with intravenous (IV) 5-fluorouracil (5-FU)–based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon and rectum. Avastin in combination with oxaliplatin and 5-FU was approved in June 2006 for second-line treatment of patients with advanced or metastatic CRC that had received prior irinotecan and 5-FU containing regimen(s).

2.2 Currently Available Treatment for Indications

The following agents are approved or in common use for the first line treatment of patients with locally advanced or metastatic NSCLC: Carboplatin, Cisplatin, Paclitaxel, Docetaxel, Gemcitabine, Vinorelbine, and Irinotecan.

2.3 Availability of Proposed Active Ingredient in the United States

Bevacizumab was approved by the U.S. Food and Drug Administration (FDA) in February 2004 for use in combination with intravenous (IV) 5-fluorouracil (5-FU)–based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon and rectum.

2.4 Important Issues With Pharmacologically Related Products

Anti-VEGF products such as α-VEGF antibodies and VEGF binding and neutralizing proteins, as well as VEGFR antagonists (TBP and small molecule drugs) are associated with some or all of the following class effect toxicities: GI perforation or GI bleeds, wound dehiscence, life threatening tumor hemorrhage, hypertension, and proteinuria.

2.5 Presubmission Regulatory Activity

Study E4599 was conducted by ECOG under the NCI's IND application (BB-IND 7921). The protocol was first submitted to the IND May 4, 2001 and activated on July, 19, 2001. There were nine addendums to the protocol. FDA responded to ECOG with a detailed letter outlining the deficiencies of the study. The following statement is excerpted from the June 5, 2003 letter to ECOG:

> *We understand that Genentech intends to utilize this study as one of several trials intended as the primary support for licensure of Bevacizumab for the treatment of metastatic colorectal cancer. However, neither you nor Genentech have met with the Agency to discuss the adequacy of this protocol to support a license application.*
>
> *Please note that in its present form, this protocol is not adequate in design to serve this purpose.*

Representatives of Genentech met with the FDA on September 2, 2004 to address changes requested by FDA to Genentech's Statistical Analysis Plan (SAP) and the adequacy of Study E4599 to support a label indication. During the September 2, 2004 meeting, FDA stated again that the Agency does not concur that Study E4599 is adequate to support the proposed use of Avastin in combination with chemotherapy for the first-line treatment of patients with advanced or metastatic non-squamous NSCLC. FDA stated that the Study could be submitted for review, but that the flawed design and variable conduct of the study limits the efficacy data that could be

used to support the proposed indication to only the survival endpoint. The secondary endpoints of response rate, duration of response, and progression free survival may not be adequate to be included in labeling because of the study deficiencies.

FDA requested ECOG audit records of the study. Audit records could not be provided. NCI/CTEP later stated during a subsequent meeting held on September 16, 2004 that the clinical site audits are too fragmentary to provide assurance of adherence to Good Clinical Practices.

Genentech provided to FDA on October 8, 2004, approximately one month prior to the planned first interim analysis, a modified SAP that was to be used for the final efficacy analysis. At the second planned interim efficacy analysis (March 2005), the DMC determined that the analysis of the primary endpoint of survival met the pre-specified criteria for statistical significance for the comparison BV/CP versus CP.

Genentech and the FDA agreed during a July 21, 2005 Type B pre-sBLA teleconference meeting that the sBLA would contain specific review data (see Appendix 3 sBLA Meeting Minutes).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

This efficacy supplement was reviewed primarily by the clinical and statistical divisions. No issues were identified that required additional consultation from other review disciplines.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of the clinical data for this review consisted of one Genentech sponsored study (AVF0757g) and one ECOG-sponsored, randomized, controlled clinical trial conducted in the USA (Study E4599).

4.3 Review Strategy

The review consisted of analysis of data from study AVF0757g and E4599.

4.4 Data Quality and Integrity

Genentech did not audit the E4599 study. Genentech, as the Applicant and beneficiary of the clinical data provided by the federal government (NCI/CTEP) sponsored study, states that all study monitoring and auditing were the responsibility of ECOG. ECOG states that ECOG sites are audited every 36 months, however, individual studies are not audited and instead a random selection of records (approximately 10%) from all the active studies at the institution are reviewed. ECOG Audit Records could not be provided to the FDA. NCI/CTEP stated during a meeting held on September 16, 2004 that the clinical site audits are too fragmentary to provide assurance of adherence to Good Clinical Practices.

The quality of E4599 adverse event data is compromised because of the limited amount of data capture and the lack of adverse event onset and ending dates. The following statement by the Applicant characterizes the lack of thoroughness of the acquisition of safety data in Study E4599:

For narratives on events leading to study discontinuation, it may not be possible to identify the exact toxicity that led to the patient's discontinuation as this information was not collected. When the event leading to study discontinuation is not apparent, the information about adverse events that may have been associated with the discontinuation will be included in the narrative. In some cases, several adverse events may be reported.

4.5 Compliance with Good Clinical Practices

The Sponsor states that Study E4599 was conducted in accordance with all Department of Health and Human Services (DHHS), Office of Human Research Protections (OHRP), and U.S. Food and Drug Administration (FDA) regulations regarding the conduct of human research. However, as noted previously, CTEP is unable to provide assurance of adherence to Good Clinical Practices, based on the NCI/CTEP monitoring and auditing practices.

The Sponsor states that Study AVF0757g was conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs) and local ethical and legal requirements.

4.6 Financial Disclosures

Financial disclosure forms are available for only 72% of the investigators (139 of 192) during the period of time from study activation, July 19, 2001 (study accrual began August 22, 2001) to March 2002. The Sponsor attempted to contact investigators by mail on two occasions to obtain financial disclosure information for this time period. None of the 139 respondents recorded a disclosure for the 6 month time period of August 2001 to March 2002. Financial information is available for 538 of 539 investigators post March 2002. Seventeen investigators reported a disclosure during this time period, resulting in a disclosure rate of 3.1%. An equity interest that exceeds $50,000 was reported by all 17 of the investigators who reported a disclosure. The 17 investigators who reported a disclosure enrolled 4% of the patients onto study. The Sponsor has demonstrated due diligence in collecting financial disclosure information. Adequate information is not available to accurately assess the impact of financial conflicts during the first 6 months of the study; however, in this reviewer's opinion, it does not appear that significant bias could have been introduced into the final results or ultimate conclusion drawn from the trial due to financial conflicts of interest.

5 CLINICAL PHARMACOLOGY

Pharmacokinetic and pharmacodynamic studies were not conducted during the E4599 clinical study. The pharmacokinetics of Avastin were previously determined from 8 different studies included in the original 125085.0 submission. Study AVF0757g included in this submission contained a small pharmacokinetic drug-drug interaction study. A Clinical Pharmacology review performed by Dr Hong Zhao identified the following concern: In Study AVF0757g, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin (PC) had substantially lower paclitaxel exposure after four cycles of treatment (at day 63) than those at day 0, while patients receiving

PC without Avastin had a greater paclitaxel exposure at day 63 than at day 0. The possible decreased paclitaxel exposure secondary to Avastin therapy will be incorporated into the Avastin Package Insert.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The current indication of Avastin is as follows: *Avastin, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.*

Genentech proposes to add to the Indications section the following: *AVASTIN in combination with platinum-based chemotherapy, is indicated for first-line treatment of patients with locally advanced, metastatic, or recurrent non–small cell lung cancer other than predominant squamous histology.*

Reviewer comment: The additional indication to the Indications Section of the Package Insert is warranted by the clinical data reviewed in Study E4599 with the following modifications: *AVASTIN, in combination with carboplatin and paclitaxel is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.*

6.1.1 Methods

The two study reports contained in this submission, Study AVF0757g and E4599, were reviewed for efficacy.

AVF0757g

Study AVF0757g is a small supporting study to E4599 and will be briefly discussed in this section.

Study AVF0757g was a randomized phase II study that compared the efficacy, safety, pharmacokinetics, and pharmacodynamics of Avastin (7.5 or 15 mg/kg) combined with carboplatin and paclitaxel (CP) chemotherapy to CP chemotherapy alone in subjects with locally advanced or metastatic (Stage IIIB with pleural effusion or Stage IV) Non-Small Cell Lung Cancer. The study was conducted over 16 months and treated 98 subjects. Crossover to Avastin was allowed at the time of documented progression. The objectives were to evaluate the efficacy, safety, and pharmacokinetics of Avastin in subjects with advanced NSCLC. The efficacy endpoints were TTP, ORR, duration of response and survival. Major eligibility criteria included the following:

- Histologically confirmed Stage IIIb (with pleural effusion), Stage IV, or recurrent NSCLC (i.e., squamous, adeno-, or large cell anaplastic carcinoma) with bi-dimensionally measurable or evaluable disease.
- ECOG performance status of 0, 1, or 2.
- Subjects were ineligible if a major surgical procedure, open biopsy, or significant traumatic injury had occurred within 4 weeks preceding Day 0.

- Subjects were ineligible if there was the anticipation of need for a major surgical procedure during the course of the study.
- Current or recent (within the 10 days preceding Day 0) use of oral or parenteral anticoagulants or aspirin was not allowed.

Subjects received up to six cycles of paclitaxel/carboplatin chemotherapy. Subjects randomized to Avastin treatment received either 7.5 or 15 mg/kg Avastin every 3 weeks in addition to paclitaxel (200 mg/m^2) and carboplatin (AUC of 6 mg/mL/min) until disease progression or for a total of 1 year of Avastin treatment if progression or unacceptable toxicity did not occur. Subjects randomized to receive paclitaxel/carboplatin alone were eligible to receive 15 mg/kg Avastin as monotherapy at the time of disease progression during the treatment or follow-up period. Avastin was continued until further disease progression, or for the remainder of the treatment period (approximately one year). Nineteen crossover subjects were treated.

Overall, 33% of subjects had received prior cancer treatment. Twenty-four percent had received prior radiation therapy, and 27% had received anticancer treatment other than or in addition to radiation (primarily consisting of surgery). More subjects in the control arm (41%) had received prior cancer treatment than in the Avastin arms (31% in the 7.5 mg/kg arm and 29% in the 15 mg/kg arm). The largest imbalance in demographic and baseline characteristics appeared in the proportion of men to women in the three treatment arms. The E4599 study results would suggest that the control arm, containing the smallest proportion of females, would be expected to have the longest duration of progression free survival and overall survival. Please see Table 1: Study AVF0757g Demographics.

Table 1: Study AVF0757g Demographics

Analysis	Control (N=32)	7.5 mg/kg (N=32)	15 mg/kg (N=35)	Total (N=99)
Sex				
Female	8 (25.0%)	12 (37.5%)	19 (54.3%)	39 (39.4%)
Male	24 (75.0%)	20 (62.5%)	16 (45.7%)	60 (60.6%)
ECOG status				
0	15 (46.9%)	16 (50.0%)	19 (54.3%)	50 (50.5%)
1	15 (46.9%)	15 (46.9%)	12 (34.3%)	42 (42.4%)
2	2 (6.3%)	1 (3.1%)	4 (11.4%)	7 (7.1%)
Duration of current cancer (yr)				
<1	22 (68.8%)	24 (75.0%)	28 (80.0%)	74 (74.7%)
1	4 (12.5%)	2 (6.3%)	4 (11.4%)	10 (10.1%)
2	2 (6.3%)	2 (6.3%)	1 (2.9%)	5 (5.1%)
≥3	4 (12.5%)	4 (12.5%)	2 (5.7%)	10 (10.1%)
Histology				
Adenocarcinoma	17 (53.1%)	20 (62.5%)	23 (65.7%)	60 (60.6%)
Large cell anaplastic	4 (12.5%)	1 (3.1%)	5 (14.3%)	10 (10.1%)
Squamous cell	7 (21.9%)	10 (31.3%)	3 (8.6%)	20 (20.2%)
Other	4 (12.5%)	1 (3.1%)	4 (11.4%)	9 (9.1%)
Cancer stage				
IIIb	6 (18.8%)	2 (6.3%)	7 (20.0%)	15 (15.2%)
IV	18 (56.3%)	23 (71.9%)	24 (68.6%)	65 (65.7%)
IV, recurrent NSCLC	0	0	1 (2.9%)	1 (1.0%)
Recurrent NSCLC	8 (25.0%)	7 (21.9%)	3 (8.6%)	18 (18.2%)

As can be seen in Table 2, the protocol defined primary endpoint of investigator-assessed tumor progression was prolonged by 96 days in the 15 mg/kg BV/CP treatment arm compared to the CP arm with a hazard ratio of 0.54 and a p-value of 0.0234. However, the Sponsor conducted an independent radiology review of the imaging data and concluded that the prolongation in time to

progression was reduced from 96 to 35 days and was no longer statistically significant with a p-value of 0.15.

Table 2: AVF0757g Progression Free Survival

	Control (N=32)	7.5 mg/kg (N=32)	15 mg/kg (N=34)
Investigator Assessment			
Progressions	27	29	29
Censored observations	5	3	5
Time to progression (days)			
Median	129.0	131.0	225.0
Hazard ratio	NA	0.89	0.54
25%–75% percentile	60.0–204.0	60.5–222.0	140.0–314.0
Range	0.0[a]– 382.0[a]	7.0–392.0[a]	22.0–379.0
95% CI (median)	(62.0, 184.0)	(63.0, 205.0)	(206.0, 303.0)
p-value (log-rank)	NA	0.6673	0.0234
IRF/Investigator Assessment			
Progressions	23	28	28
Censored observations	9	4	6
Time to disease progression (days)			
Median	181.0	108.0	213.0
Hazard ratio	NA	1.13	0.67
25%–75% percentile	58.0–212.0	57.0–219.0	62.0–359.0
Range	0.0[a]–382.0[a]	7.0–399.0[a]	9.0–400.0[a]
95% CI (median)	(102.0, 211.0)	(60.0, 198.0)	(169.0, 301.0)
p-value (log-rank)	NA	0.6763	0.1524

Table 3 shows the investigator- and independent radiology review- assessed objective response rates for Study AVF0757g. The investigator-assessed response rate in the 15 mg/kg treatment arm versus the control arm yielded a two-sided-p value of 0.27. The IRF (cavitation) assessment was an additional, non-prespecified radiological evaluation of response developed after initial review of the imaging assessments. There was no evidence for a survival benefit with Avastin, however, 19 of 32 patients randomized to the control arm crossed over to receive Avastin following disease progression.

Table 3: AVF0757g Objective Response Rates

Source	Control (N=32)	7.5 mg/kg (N=32)	15 mg/kg (N=35)
Investigator	6 (18.8%)	9 (28.1%)	11 (31.5%)
IRF/investigator	10 (31.3%)	7 (21.9%)	14 (40.0%)
IRF (cavitation)/investigator	10 (31.3%)	8 (25.0%)	18 (51.4%)

STUDY E4599

In study E4599, clinical efficacy in the primary endpoint of duration of survival was compared between the BV/CP and CP treatment arms. The efficacy endpoints (duration of survival, progression free survival, and objective response) were analyzed, and subgroup analyses for the primary efficacy endpoint of duration of survival were performed. The FDA statistical reviewer confirmed the primary efficacy analyses.

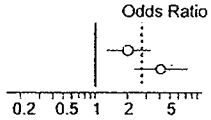
6.1.2 General Discussion of Endpoints

The primary endpoint (outcome measure) for Study E4599 was duration of survival. The use of the primary endpoint in this study was acceptable. The Genentech statistical analysis plan included progression-free survival, objective response, and duration of objective response as secondary efficacy endpoints. The primary endpoint in this submission was adequate for

allowing the evaluation of the relative efficacy of BV/CP compared to CP alone in prolonging the duration of clinically meaningful survival. Although overall the secondary endpoints of objective response rate and progression free survival support the primary endpoint, these secondary outcome measures are more susceptible to the introduction of bias as the study was not blinded and did not employ prespecified imaging acquisition parameters or a centralized blinded review of source imaging data. In addition, upon exploratory subgroup analyses, female sex (representing 46% of the patients enrolled on study) revealed no survival advantage, yet the odds ratio for objective response was 4.04 in females versus 2.01 in males as seen below.

E4599: Objective Response by Other Exploratory Variables
(Randomized Patients with Measurable Disease)

		CP (n=403)		BV/CP (n=397)			
Baseline Characteristic	Total n	Response n	(%)	Response n	(%)	Odds Ratio	(95% CI)
Sex							
Male	436	235	(14.5)	201	(25.4)	2.01	(1.24 - 3.26)
Female	364	168	(10.7)	196	(32.7)	4.04	(2.28 - 7.16)



The E4599 protocol itself, in a description of the AVF0757g study results, documents the changes that can occur to endpoints that require detailed interpretation by expert clinicians when the data are reevaluated by blinded review committees as can be seen in the table below (Reproduced from the E4599-A9 protocol).

Table 2

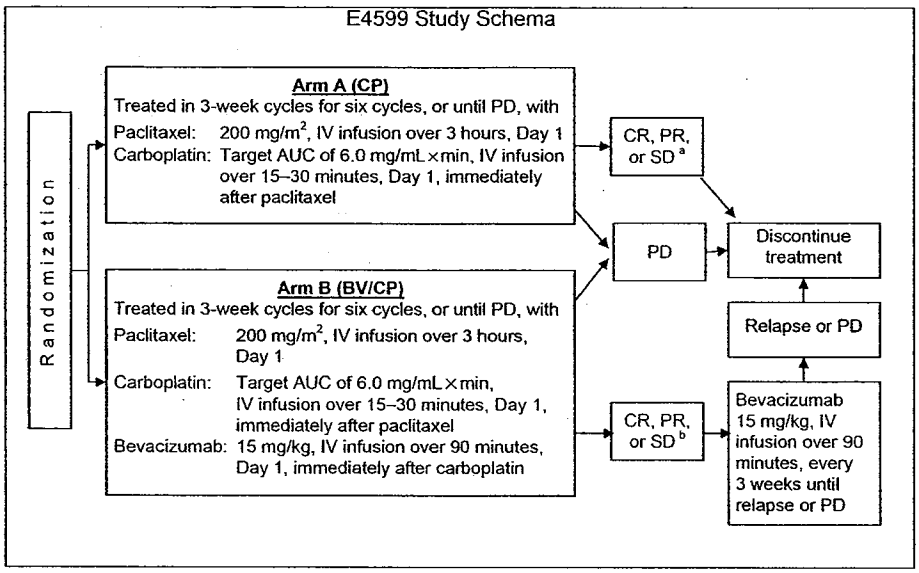
Updated Results of Randomized Phase II Trial of Bevacizumab in Advanced NSCLC

	Group:	Control:	7.5 mg/kg:	15 mg/kg:	p-value:
ORR:	Investigator	18.8%	28.1%	31.4%	NS
	Independent Review Board	25%	21.9%	34.2%	NS
TTP:	Investigator	18.4 wk	18.7 wk	32.1 wk	0.023 (v. ctrl) 0.043 (v. 7.5)
	Independent Review Board	25.8 wk	17.7 wk	29.6 wk	0.32 (v. ctrl) 0.44 (v. 7.5)
MST:	All	56.8 wk	49.9 wk[1]	61.5 wk	NS

6.1.3 Study Design

Study E4599 was an open label, randomized 1:1, phase 3, multicenter, controlled trial to evaluate the efficacy and safety of BV/CP versus CP in chemotherapy naive patients with advanced or metastatic non-squamous NSCLC. The study was conducted by the Eastern Cooperative Oncology Group (ECOG) and carried out at 254 sites in the United States and two non-US sites. Eight hundred seventy eight patients were randomized and enrolled on study from August 22, 2001 to April 8, 2004. The following schematic in Figure 1 and study outline below summarize the E4599 Study design:

Figure 1 E4599 Study Schematic



STUDY OUTLINE

Objectives

Primary:

- To assess toxicity and overall survival in patients with previously untreated locally advanced or metastatic (Stage IIIb with malignant pleural effusion or Stage IV or recurrent) NSCLC (excluding NSCLC categorized as squamous cell) treated with carboplatin/paclitaxel ± bevacizumab.

Secondary:

- To assess response rates and time to progression in patients with advanced or metastatic (stage IIIB-pleural effusion/IV), nonsquamous histology NSCLC treated with carboplatin plus paclitaxel ± bevacizumab.

Study Population

Eligibility Criteria

- Histologically or cytologically confirmed non-small cell lung cancer EXCEPT squamous cell carcinoma. Mixed tumors will be categorized by the predominant cell type unless small cell elements are present in which case the patient is ineligible. Cytologic or histologic elements can be established on metastatic tumor aspirates or biopsy.
- Advanced NSCLC (stage IIIb with malignant pleural effusion or Stage IV or recurrent disease).
- Measurable or non-measurable disease.
- ECOG performance status 0 or 1.
- No known CNS metastases. A head CT was required within 4 weeks prior to study entry. (MRIs were also acceptable)
- Patients must not have received prior systemic chemotherapy at any time.
- Required laboratory values (obtained < 1 week prior to randomization):
  - ANC > 1500/mm³

- Platelets > 100,000/mm³
- Total Bilirubin < 1.5 mg/dl
- Transaminases < 5 x ULN.

- Patients must have had adequate renal function as determined by the following tests within 1 week prior to randomization.
  - Serum creatinine less than or equal to 1.5 x upper limit of normal (ULN), AND
  - Urine dipstick for proteinuria of less than 1+ (i.e., either 0 or trace). If urine dipstick is > 1+ then a 24 hour urine for protein must have demonstrated < 500 mg of protein in 24 hours to allow participation in the study.
- 18 years or older.
- INR < 1.5 and a PTT no greater than the upper limit of normal within 1 week prior to randomization.
- Pregnant and lactating women were excluded from the study.
- Women of childbearing potential and sexually active males must have agreed to use an accepted and effective method of contraception (hormonal or barrier methods, abstinence) prior to study entry and for the duration of the study.
- No immuno, hormonal or radiation therapy within 3 weeks prior to entering the study. Those who had not recovered from adverse events due to agents administered more than 3 weeks earlier were ineligible.
- Patients were not to have had ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- No history of thrombotic or hemorrhagic disorders.
- Patients with a history of hypertension were to be well-controlled (<150/100) on a stable regimen of anti-hypertensive therapy.
- Patients were not to be receiving chronic daily treatment with aspirin (> 325 mg/day) or nonsteroidal anti-inflammatory agents known to inhibit platelet function. Treatment with dipyridamole (Persantine), ticlopidine (Ticlid), clopidogrel (Plavix) and/or cilostazol (Pletal) was not allowed.
- Patients were not to have had serious non-healing wound ulcer, or bone fracture, or major surgical procedure within 21 days prior to starting treatment.
- Patients were not to have been on therapeutic anticoagulation. Prophylactic anticoagulation of venous access devices was allowed.
- Patients with a history of gross hemoptysis (defined as bright red blood of a ½ teaspoon or more) were excluded from this trial.

Treatment Plan

- Protocol therapy (CP or BV/CP) was given in repeating 3-week cycles for a total of 6 cycles.
- Treatment with bevacizumab was to be continued until disease progression or unacceptable toxicity.

Dose Reduction and Discontinuation

- Bevacizumab treatment was to be modified if a patient experienced any of the following types and grades (per NCI-CTC v2) of adverse events:
    - Hemorrhage
        - For a < Grade 2 event, bevacizumab was to be held until the event resolved and then resumed at 15 mg/kg. If a second Grade 2 or greater event occurred, bevacizumab was to be permanently discontinued.
        - For a Grade 2, 3 or 4 event, bevacizumab was to be permanently discontinued.
    - Hemoptysis
        - Hemoptysis: > Grade 1, patient's protocol treatment was to be discontinued. For Grade 1, patients should have been evaluated to determine the source of hemoptysis. If no source was found, and the bleeding resolved within 1 week, bevacizumab treatment was to be resumed at 15 mg/kg
    - Proteinuria
        - For a urine dipstick protein result of 1 + or greater, bevacizumab was to be held and a 24-hr urine collection for protein measurement performed:
        - If the 24-hour protein measurement was $\leq$ 2000 mg, bevacizumab dosing was not modified
            - If the 24-hour protein measurement was > 2 g, bevacizumab was to be held until the 24-hour protein measurement resolved to $\leq$ 2 g; bevacizumab was then to be resumed at 15 mg/kg.
    - Liver function test elevation (AST, ALT, alkaline phosphatase, and total bilirubin)
        - For a Grade 3 or 4 event, bevacizumab was to be held until the event resolved to Grade $\leq$ 1 and then resumed at 15 mg/kg.
        - If a Grade 3 or 4 event recurred, bevacizumab was to be permanently discontinued.
    - Coagulopathy
        - Patients who develop any thrombotic event requiring systemic anticoagulation will discontinue protocol treatment.
    - Hypertension
        - Bevacizumab was to be discontinued for uncontrolled or symptomatic hypertension.
    - Arterial thromboembolic events(including cerebrovasular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia):
        - > Grade 3: discontinue bevacizumab
        - Grade 2, if new or worsen since bevacizumab therapy, discontinue bevacizumab

Tumor response and disease progression

- Response and progression were assessed by the ECOG Coordinating Center based on a review of tumor assessments provided by the investigator.

- Tumor evaluations were performed according to the Response Evaluation Criteria in Solid Tumors (RECIST).
    - While on protocol therapy, tumor assessments were performed every two cycles of treatment or approximately every 6 weeks.
    - After 6 cycles of treatment the tumor assessment frequencies were different between treatment arms. Patients in the BV/CP arm were evaluated every three cycles or 9 weeks whereas patients on the CP arm underwent tumor assessments every 3 months.
- Subjects were followed for survival status until death.

Safety Conduct

- NCI CTC v 2.0 was used to describe and grade adverse events.
- Adverse events were recorded over discrete time periods; the onset date of the adverse event was not recorded. The discrete time period durations were to range from every three weeks to every nine weeks.

  The reporting period, as documented in the Case Report Tabulations, ranged from 1-392 days (median 21).
- All Grade 4 and 5 hematologic and Grade 3-5 non-hematologic adverse events regardless of investigator determined attribution to protocol therapy were required to be reported on the CRFs.
- ECOG or other cooperatives did not provide any guidance as to the manner and frequency in which subjects were queried regarding adverse events and instead each site was to follow their institution's process.
- Adverse events that required expedited reporting on the BV/CP arm were reported to NCI's Adverse Event Expedited Reporting System (NCI AdEERS) as specified in the protocol.
- Adverse events that led to bevacizumab discontinuation were not identified.
- The Sponsor notes multiple limitations of the ECOG narratives and states the following:

  For narratives on events leading to study discontinuation, it may not be possible to identify the exact toxicity that led to the patient's discontinuation as this information was not collected. When the event leading to study discontinuation is not apparent, the information about adverse events that may have been associated with the discontinuation will be included in the narrative. In some cases, several adverse events may be reported..

Statistical and Analytical Plan

Refer to statistical analysis and review by Yuan Li Shen, Ph.D., Mathematical Statistician for a detailed review.

Efficacy Variables

Stratified randomization was performed based on the following stratification factors:

- Measurable disease (yes vs. no);
- Prior radiation therapy (yes, vs. no);
- Degree of weight loss over the previous 6 months (<5% vs. ≥5%);
- Disease stage (stage IIIb with pleural effusion vs. stage IV vs. recurrent).

The primary analysis of each of the efficacy endpoints was carried out on the ITT population.

- The primary efficacy endpoint for this study was duration of survival (Date of randomization to date of death from any cause).
    - Duration of survival was formally compared between the BV/CP and CP arms using the two-sided stratified log-rank test and are also presented using Kaplan-Meier methodology.
    - The hazard ratio for death on the BV/CP arm relative to the CP arm was estimated using a stratified Cox regression model with an indicator variable for bevacizumab treatment.
    - The Type I error rate for the comparison of the principal arms for the primary endpoint of duration of survival was controlled at $\alpha = 0.05$ (two-sided). To control the Type I error rate for the primary endpoint of duration of survival based on the sequential interim analysis testing, the Lan and DeMets implementation of the O'Brien-Fleming α-spending function was used.
    - The effects of demographic and baseline prognostic characteristics on duration of survival were examined for the principal treatment arms as exploratory analyses. The following demographic and baseline characteristics were considered:
        - ECOG performance status at study entry (0, = 1)
        - Prior radiation therapy (yes, no)
        - Age (< 40, 40–65, > 65 years)
        - Sex
        - Histologic type
        - Stage (stage IIIB with Pleural effusion, Stage IV, recurrent)
        - Race (White, non-White)
        - Weight loss in the previous 6 months (<5%, ≥5%)
        - Baseline sum of the longest diameters of target lesions (greater than or equal to median, less than median).
    - A multivariate analysis of risk factors was performed.
- Secondary efficacy endpoints were based only on radiological evidence and consisted of the following:
    - Progression-Free Survival, defined as the time from randomization to disease progression or to death from any cause within 30 days following discontinuation of protocol therapy. Data for patients who discontinue all study treatment prior to disease progression were censored at the time of the last tumor assessment prior to discontinuation.
    - Objective Response, defined as a complete or partial best confirmed response (CR or PR) as assessed by the ECOG Coordinating Center using RECIST. Objective response rates were formally compared between the principal treatment arms using the Cochran-Mantel-Haenszel test. An estimate of objective response rate and its 95% confidence interval (CI) were determined.
    - Duration of Objective Response, defined as the time from the first tumor assessment that met the criteria for objective response to the time of disease progression or death from any cause within 30 days following discontinuation of protocol therapy.

Amendments to Protocol

Please see Appendix 1 for a brief description of substantive changes for each protocol amendment as described in the respective ECOG Clinical Research Associates Addendum Letters.

6.1.4 Efficacy Findings

6.1.4.1 Study Conduct

Eight hundred and seventy eight patients were randomized (444 patients to the CP arm and 434 patients to the BV/CP arm) on this study between August 22, 2001 and April 8, 2004. Eight hundred and sixty eight patients received at least one component of protocol therapy. A total of 256 centers randomized subjects into this study. Enrollment by center ranged from 1 to 28 patients. For a summary of subject disposition see Table 4: Subject Disposition (reproduced from the CSR section 10.1, page 62).

Table 4: Subject Disposition

E4599: Patient Disposition and Reason for Study Treatment Discontinuation: Randomized Patients

	CP (n=444)	BV/CP (n=434)	Total (n=878)
Treated	441 (99.3%)	427 (98.4%)	868 (98.9%)
Not known to have discontinued protocol therapy	0 (0.0%)	1 (0.2%)	1 (0.1%)
Treatment completed per protocol	185 (41.7%)	5 (1.2%)	190 (21.6%)
Discontinued protocol therapy	256 (57.7%)	421 (97.0%)	677 (77.1%)
Reason not stated [a]	8 (1.8%)	35 (8.1%)	43 (4.9%)
Discontinued as per protocol	152 (34.2%)	266 (61.3%)	418 (47.6%)
Disease progression during active treatment [b]	135 (30.4%)	239 (55.1%)	374 (42.6%)
Death on study	17 (3.8%)	27 (6.2%)	44 (5.0%)
Premature withdrawal from protocol treatment	96 (21.6%)	120 (27.6%)	216 (24.6%)
Toxicity/side effects/complications [c]	57 (12.8%)	82 (18.9%)	139 (15.8%)
Patient withdrawal or refusal	17 (3.8%)	9 (2.1%)	26 (3.0%)
Alternative therapy	7 (1.6%)	3 (0.7%)	10 (1.1%)
Other complicating disease	4 (0.9%)	1 (0.2%)	5 (0.6%)
Other	11 (2.5%)	25 (5.8%)	36 (4.1%)
Not Treated	3 (0.7%)	7 (1.6%)	10 (1.1%)
Known to have no treatment	2 (0.5%)	5 (1.2%)	7 (0.8%)
Patients with no treatment information	1 (0.2%)	2 (0.5%)	3 (0.3%)

BV/CP = bevacizumab + carboplatin/paclitaxel; CP = carboplatin/paclitaxel.

Notes: Patients in the BV/CP arm were treated until progression or important toxicity, whereas patients in the CP arm were treated for six cycles. Percentages were computed relative to the number of randomized patients.

[a] "Reason not stated" category within the "discontinued protocol therapy" group includes patients who have no discontinuation reason but have indication that the protocol therapy has stopped.

[b] The most common reason for study discontinuation other than treatment completed per protocol on or before Cycle 6 was disease progression (133/440 [30.2%] in the CP arm and 75/429 [17.5%] in the BV/CP arm

[c] The number of patients who discontinued the study due to toxicity/side effects/complications prior to or at Cycle 6 was nearly identical in the two arms (57/440 [13.0%] in the CP arm and 60/429 [14.0%] in the BV/CP arm

Genentech states that ECOG was responsible for assessing all protocol deviations except for the use of non-protocol anti-tumor therapy. Protocol deviations appear to have been assessed by ECOG

based on the ECOG-Case Evaluation Form and Eligibility Evaluation form. The CP arm had 274 out of 444 (61%) patients and the BV/CP arm 233 out of 434 (54%) patients who had Case Evaluation Forms completed and available for ECOG review. Eligibility Forms were available for 91% of the patients on the CP arm and 90% of the patients on the BV/CP arm. Nine subjects were enrolled in the Expanded Participation Program for which information on non-protocol anti-tumor therapy prior to progression was not collected. The primary minor protocol deviation (as assessed by Genentech) was administration of non-protocol anti-tumor therapy prior to progression. Non-protocol anti-tumor therapy administered prior to disease progression, consisting primarily of chemotherapy, was used in 18% of patients on the CP arm and 13% of patients on the BV/CP arm.

Reviewer Comment: *The lack of complete assessment of protocol deviations, as described above, is concerning in relation to acquisition of trial data as a whole.*

6.1.4.2 Study Demographics.

The baseline demographic and disease characteristics of the study subjects are shown in . The mean age of patients was 62 years, 54% of patients were male, and 85% of patients were Caucasian. The baseline characteristics of the study arms were similar except that the CP arm had a higher proportion of males (58%) compared with the BV/CP arm (50%). Approximately 19% of patients had prior surgery and 9% of patients had prior radiotherapy. There were no known clinically relevant baseline imbalances between study arms except for a 3% higher proportion of patients with Stage IV disease on the CP arm. There was a statistically significant difference in the survival between patients with recurrent disease and patients with Stage 4 disease; however, a multivariate Cox model analysis including disease stage still resulted in a hazard ratio of 0.83 favoring bevacizumab plus CP with a p-value of 0.0191. This suggests that the imbalance in Stage IV disease between treatment arms, although biasing the study results, was not a driving factor for the observed treatment effect and does not alter the final efficacy conclusions. There were 18 (4%) additional subjects on the CP arm that had unfavorable tumor histology based on an exploratory analysis for factors affecting survival.

6.1.4.3 Primary Analyses

The primary efficacy endpoint for this study was duration of survival. Duration of survival was defined as the time from randomization to death from any cause. All reported deaths were included in the analysis. Duration of survival for patients who were not known to have died at the time of analysis was censored at the date the patient was last known to be alive. The first interim analysis was performed on November 2, 2004 based on a data cutoff date of September 7, 2004. At the time of the second interim analysis, conducted on March 9, 2005 based on a data cutoff data of February 9, 2005, 112 patients were censored that had actually died before the data cutoff date for the analysis. The second interim analysis of the study data showed that the pre-specified criteria for statistical significance had been met. FDA used the February 2005 data cutoff date for performing the March 2005 analysis, but included the 112 deaths missed by the ECOG analysis and censoring mechanisms in determining nominal and final significance values. For descriptive purposes the following information is derived from the updated December 2005 data base cutoff, however, the p-value is derived from the FDA ITT reanalysis of the second ECOG interim analysis. The median duration of survival was increased from 10.3 months in the CP arm to 12.3 months in the BV/CP arm with a nominal p-value of 0.0134. The stratified hazard ratio for death for the BV/CP arm relative to the CP arm was 0.80 (95%CI: 0.68, 0.94)

{See Table 7 Adapted from Table 11 of the CSR}. A worse-case sensitivity analysis whereby subjects lost to follow-up on the BV/CP arm were considered to have experienced death while patients lost to follow-up on the CP arm were censored at the date of last known contact showed that duration of survival was improved in the BV/CP arm compared with the CP arm (hazard ratio 0.870 {95% CI [0.751, 1.008]}), however the survival advantage does not hold with a nominal p-value of 0.062. It is noted that approximately 8% of patients on each study arm were assessed as ineligible by ECOG but were included in the ECOG prespecified "per protocol" efficacy analyses. The Applicant's efficacy analyses were conducted on the ITT population.

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Table 6: Baseline Demographics and Disease Characteristics

E4599: Demographic Characteristics: Randomized Patients

	CP (n = 444)	BV/CP (n = 434)	Total (n = 878)
Age (years)			
n	444	434	878
Mean (SD)	62.0 (9.8)	62.3 (10.4)	62.2 (10.1)
Median	63.0	63.0	63.0
Range	32–82	27–88	27–88
Age category (years)			
n	444	434	878
<40	4 (0.9%)	9 (2.1%)	13 (1.5%)
40-64	246 (55.4%)	240 (55.3%)	486 (55.4%)
≥65	194 (43.7%)	185 (42.6%)	379 (43.2%)
Sex			
n	444	434	878
Male	259 (58.3%)	219 (50.5%)	478 (54.4%)
Female	185 (41.7%)	215 (49.5%)	400 (45.6%)
Race			
n	444	434	878
Asian	3 (0.7%)	5 (1.2%)	8 (0.9%)
Black	24 (5.4%)	23 (5.3%)	47 (5.4%)
Filipino	1 (0.2%)	0 (0.0%)	1 (0.1%)
Hispanic	8 (1.8%)	9 (2.1%)	17 (1.9%)
Indian (Asian)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Native American	2 (0.5%)	1 (0.2%)	3 (0.3%)
White	387 (87.2%)	366 (84.3%)	753 (85.8%)
Other [a]	19 (4.3%)	29 (6.7%)	48 (5.5%)

E4599: Disease Characteristics at Study Entry: Randomized Patients

	CP (n=444)	BV/CP (n=434)	Total (n=878)
ECOG performance status (baseline)			
n	443	431	874
0	175 (39.5%)	171 (39.7%)	346 (39.6%)
1	268 (60.5%)	260 (60.3%)	528 (60.4%)
Disease stage			
n	443	433	876
IIIb	56 (12.6%)	52 (12.0%)	108 (12.3%)
IV + Recurrent	387 (87.4%)	381 (88.0%)	768 (87.7%)
IV	345 (77.9%)	324 (74.8%)	669 (76.4%)
Recurrent	42 (9.5%)	57 (13.2%)	99 (11.3%)
Measurable disease			
n	444	433	877
No	41 (9.2%)	36 (8.3%)	77 (8.8%)
Yes	403 (90.8%)	397 (91.7%)	800 (91.2%)
Body weight loss in previous 6 months			
n	443	428	871
< 5%	316 (71.3%)	308 (72.0%)	624 (71.6%)
≥5%	127 (28.7%)	120 (28.0%)	247 (28.4%)
5 to < 10%	80 (18.1%)	75 (17.5%)	155 (17.8%)
10 to < 20%	37 (8.4%)	34 (7.9%)	71 (8.2%)
≥ 20%	10 (2.3%)	11 (2.6%)	21 (2.4%)

E4599: Baseline Tumor Characteristics—Randomized Patients

	CP (n=444)	BV/CP (n=434)	Total (n=878)
Histological type			
n	442	433	875
Adenocarcinoma	302 (68.3%)	300 (69.3%)	602 (68.8%)
Squamous	2 (0.5%)	1 (0.2%)	3 (0.3%)
Large cell undifferentiated	30 (6.8%)	18 (4.2%)	48 (5.5%)
Bronchioloalveolar (BAC)	11 (2.5%)	12 (2.8%)	23 (2.6%)
NSCLC, NOS	86 (19.5%)	79 (18.2%)	165 (18.9%)
Other	11 (2.5%)	23 (5.3%)	34 (3.9%)
Site of metastases			
Any site	422 (95.0%)	414 (95.4%)	836 (95.2%)
Hilar nodes	164 (36.9%)	176 (40.6%)	340 (38.7%)
Mediastinal nodes	228 (51.4%)	228 (52.5%)	456 (51.9%)
Supraclavicular/scalene nodes	37 (8.3%)	34 (7.8%)	71 (8.1%)
Ipsilateral lung	188 (42.3%)	177 (40.8%)	365 (41.6%)
Contralateral lung	145 (32.7%)	147 (33.9%)	292 (33.3%)
Pleura	111 (25.0%)	112 (25.8%)	223 (25.4%)
Liver	74 (16.7%)	93 (21.4%)	167 (19.0%)
Adrenal(s)	75 (16.9%)	54 (12.4%)	129 (14.7%)
Bone	156 (35.1%)	126 (29.0%)	282 (32.1%)
Bone marrow	2 (0.5%)	3 (0.7%)	5 (0.6%)
Skin	9 (2.0%)	4 (0.9%)	13 (1.5%)
Pleural effusion present			
n	444	433	877
Yes	169 (38.1%)	164 (37.9%)	333 (38.0%)
No	275 (61.9%)	269 (62.1%)	544 (62.0%)
Number of metastatic sites (baseline)			
n	444	433	877
<4	320 (72.1%)	311 (71.8%)	631 (71.9%)
≥4	124 (27.9%)	122 (28.2%)	246 (28.1%)

E4599: Prior Cancer Treatment: Randomized Patients

	CP (n=444)	BV/CP (n=434)	Total (n=878)
Prior radiotherapy			
n	444	431	875
No	403 (90.8%)	392 (91.0%)	795 (90.9%)
Yes	41 (9.2%)	39 (9.0%)	80 (9.1%)
Prior surgery			
n	444	431	875
No	368 (82.9%)	343 (79.6%)	711 (81.3%)
Yes	76 (17.1%)	88 (20.4%)	164 (18.7%)
Prior chemotherapy			
n	444	431	875
No	444 (100.0%)	430 (99.8%)	874 (99.9%)
Yes	0 (0.0%)	1 (0.2%)	1 (0.1%)
Prior systemic therapy			
n	444	427	871
No	444 (100.0%)	423 (99.1%)	867 (99.5%)
Yes	0 (0.0%)	4 (0.9%)	4 (0.5%)

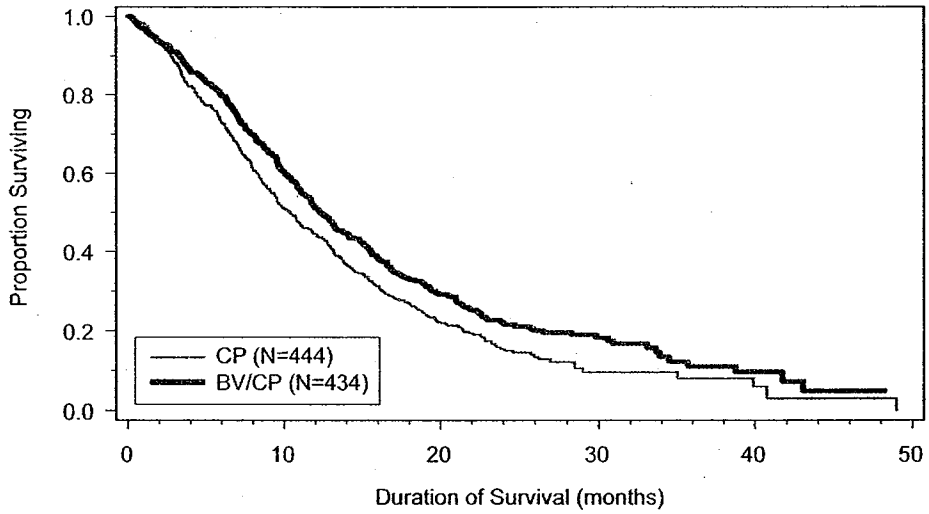
Table 7: Duration of Survival (Randomized Subjects)

	CP (n=444)	BV/CP (n=434)
Subjects who died	363	335
Subjects alive	81 (18.2%)	99 (22.8%)
Duration of survival (mo)		
Median	10.3	12.3
95% CI	(9.36, 11.73)	(11.30, 13.73)
Stratified analysis		
Hazard Ratio[a]	NA	0.80
95% CI	NA	(0.68, 0.94)
p-value (log-rank)	NA	0.013

CI = confidence interval; NA= not applicable
[a] Relative to CP. The strata are tumor measurability, weight loss (<5%, ≥5%), stage (IIIb vs IV or recurrent) and prior radiotherapy (yes, no).

A Kaplan-Meier duration of survival estimate is provided in Figure 2: Kaplan-Meier Estimate of Duration of Survival (Randomized Subjects) and is adapted from Figure 3 of the CSR.

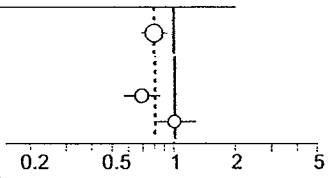
Figure 2: Kaplan-Meier Estimate of Duration of Survival (Randomized Subjects)



A multivariate Cox Model analysis was performed to estimate the effect of bevacizumab after adjusting for important prognostic factors (Weight loss, ECOG PS, Gender, Baseline sum of longest diameters of tumor, and Stage). The adjusted hazard ratio indicated a 17% reduction in the hazard of death among patients in the BV/CP arm compared to patients in the CP arm. In addition, the point estimate hazard ratios for the pre-specified stratification factors were all less than 1 favoring the BV/CP arm. Despite the multivariate Cox analysis showing that there was still a bevacizumab treatment effect in prolonging the duration of survival, accounting for gender, the simple analysis by gender result is still striking and unexplained in that the hazard ratio comparing duration of survival of BV/CP to CP in females was 0.99 (95%CI {0.79-1.25}) as seen below in the Sponsor provided diagram.

E4599: Duration of Survival
by Baseline Characteristics for Other Exploratory Variables

Baseline Characteristic	Total n	CP (n=444) Median n (months)	BV/CP (n=434) Median n (months)	Hazard Ratio (95% CI)
All patients	878	444 10.3	434 12.3	0.80 (0.69 - 0.93)
Sex				
Male	478	259 8.9	219 11.7	0.69 (0.57 - 0.85)
Female	400	185 13.2	215 13.3	0.99 (0.79 - 1.25)



Females on the BV/CP arm had an ORR rate of 32.7 percent compared to males on the BV/CP arm with an ORR of 25.4 %. Females on the BV/CP arm appear to have received a treatment effect from bevacizumab in PFS, but the effect was not as great as that seen in males.

There were no imbalances in baseline demographic characteristics that could account for the apparent lack of survival benefit seen in the female subgroup, although there was an 8% higher rate of > 5% weight loss in the female subgroup in the BV/CP arm. The distributions of race, age, prior radiotherapy, ECOG PS, measurable disease at baseline, and histology were similar between males and females and between treatment groups for both males and females. Females had a higher rate of non-protocol therapy prior to progression. The rate of any non-protocol next-line therapy after progression was slightly higher for males.

Quantitative exposure data on the CP components administered to subjects were not collected in Study E4599. Adequate assessment for the possible confounding effects of unequal exposure to CP chemotherapy on the duration of survival between treatment arms cannot be performed. However, during the first 6 cycles of therapy there were 0.96 dose modifications/6 cycles/patient (95% CI: 1.08, 0.84) in the BV/CP arm compared to 0.58 (95% CI: 0.67, 0.49) dose modifications in the CP arm. It is not possible, based on the data sets provided for review, to determine if the dose modifications represent dose reductions or which component of the regimen was altered, however, it appears that more dose reductions were likely to have occurred on the BV/CP arm during the first 6 cycles of chemotherapy. The asymmetry noted in dose modifications during the first 6 cycles of chemotherapy is not likely to have favored the BV/CP arm.

6.1.4.4 Secondary Analyses

The PFS and OR data from study E4599 are more susceptible to the introduction of bias then the survival endpoint for the following reasons:

1. The study was not blinded.
2. The study used investigator derived tumor assessment measurements for determination of response.
3. The study did not employ an independent blinded radiology review charter.
4. The study did not utilize a standard operating procedure for imaging acquisition and archiving.

Progression Free Survival

The analysis population for PFS included all randomized patients. PFS was defined as the time from randomization to disease progression or to death from any cause. The following patients

were censored at the time of the last tumor assessment: patients without disease progression or death at the time of analysis, patients who received non-protocol anti-tumor therapy prior to experiencing disease progression and patients who discontinued all study treatment secondary to toxicity prior to disease progression.

A stratified analysis of PFS for all patients randomized revealed an increase in PFS in patients on the BV/CP arm compared to patients on the CP arm ($p < 0.0001$). Median PFS was 6.4 months in the BV/CP arm and 4.8 months in the CP arm. The stratified hazard ratio for disease progression or death for BV/CP relative to CP was 0.65 (95% CI: 0.56, 0.76) see Table 8: Progression-Free Survival (Randomized Subjects) adapted from Table 16 of the CSR. Kaplan-Meier curves for PFS are shown in Figure 3: Kaplan-Meier Estimate of Progression-Free Survival (Randomized Subjects).

Since censoring of subjects who received non-protocol anti-tumor therapy may represent informative censoring, the FDA statistical reviewer performed a worse case sensitivity analysis whereby subjects in the BV/CP arm who started non-protocol anti-tumor therapy prior to disease progression were considered to have had a progression event at the time non-protocol anti-tumor therapy was initiated, while subjects in the CP arm were censored at the time of non-protocol anti-tumor therapy. This worse case sensitivity analysis of PFS, as can be seen below, did not change the results of the study.

PFS Sensitivity analysis (worse case)

Treatment Arm	**BV/CP** (n=434)	**CP** (n=444)
No. patients with an event	394 (90.8%)	348 (78.4%)
Median PFS (months)	5.9	4.8
(95% CI)	(5.4, 6.3)	(4.4, 5.4)
Hazard ratio (relative to CP)	0.78	
(95% CI)	(0.67, 0.90)	
p-value (log rank)	0.001	

The frequency of imaging assessments was the same for both treatment arms through the first 6 cycles of therapy (18 weeks), after that patients on the CP arm had tumor assessments every three months while patients on the BV/CP arm underwent tumor assessments every 9 weeks. This tumor assessment ascertainment bias would have favored the CP arm and would not likely have been a factor in the prolonged PFS seen in the BV/CP arm compared to the CP arm.

In order to evaluate duration of PFS in a manner that was not affected by the asynchronous assessment schedules, the Sponsor performed landmark PFS analyses at 13 weeks and 19 weeks. At 13 weeks, patients in the BV/CP arm had a PFS rate 12.4% higher than patients in the CP arm $p < 0.0001$), and at 19 weeks this difference was 14.4% ($p < 0.0001$)

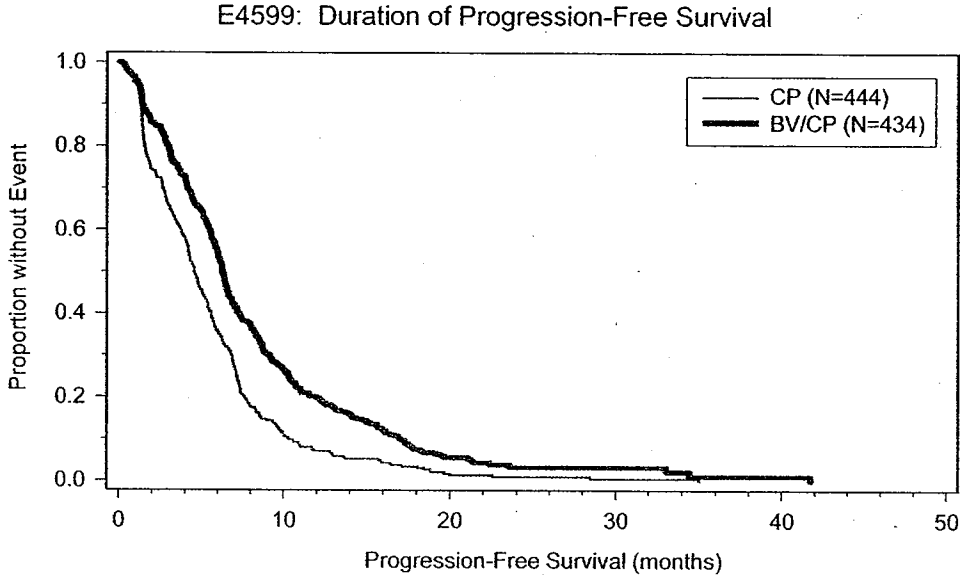
Table 8: Progression-Free Survival (Randomized Subjects)

Treatment Arm	**BV/CP** (n=434)	**CP** (n=444)
Subjects with an event	341 (78.6%)	348 (78.4%)
Disease progression	247 (72.4%)	273 (78.4%
Death	94 (27.6%)	75 (21.6%)
Censored observations	93	96
Progression-free survival		
Median (months)	6.4	4.8

Treatment Arm	BV/CP (n=434)	CP (n=444)
95% CI	(6.11, 6.87)	(4.40, 5.39)
Stratified analysis		
Hazard ratio[a]	0.65	NA
95% CI	(0.56, 0.76)	NA
p-value (log-rank)	< 0.0001	NA

CI = confidence interval; NA= not applicable
[a] Relative to BV/CP The strata are tumor measurability (yes vs. no), prior radiotherapy (yes vs. no), weight loss (< 5% vs. ≥ 5%), and stage (IIIb or IV or recurrent)

Figure 3: Kaplan-Meier Estimate of Progression-Free Survival (Randomized Subjects)



BV/CP=bevacizumab+carboplatin/paclitaxel; CP=carboplatin/paclitaxel.

Objective Response Rate

The population analyzed for the secondary efficacy endpoint of objective response rate consisted of all randomized patients with measurable disease. The analysis of duration of objective response included a subset of randomized subjects and was therefore characterized only in descriptive terms and not subjected to formal hypothesis testing.

The objective response rate for randomized subjects with measurable disease at baseline was higher ($p < 0.0001$) in the BV/CP arm (29.0%) than in the CP arm (12.9%) {See Table 9: Objective Response (Randomized Subjects)}. The majority of objective responses reported were PRs. The median duration of objective response was 6.2 months in the BV/CP arm compared to 5.0 months in the CP arm.

Table 9: Objective Response (Randomized Subjects)

Treatment Arm	BV/CP (n=397)	CP (n=403)
Objective response (%)	115 (29.0%)	52 (12.9%)
95% CI	(24.6%, 33.7%)	(9.9%, 16.7%)
Difference in objective response rate		
BV/CP-CP	16.1%	
(95% CI)	(10.5%, 21.6%)	
p-value	< 0.0001	

Although Study E4599 met the primary endpoint of prolonging survival, the results of the analyses for progression-free survival and objective response are less definitive as these endpoints are more susceptible to the introduction of bias. Assessment of radiographic images for determination of tumor response requires detailed interpretation by expert clinicians. Differences in evaluation of radiological source data can critically affect the reported results of progression-free survival and objective response. At a minimum, the FDA expects that such interpretations are made blindly, whether conducted by investigators or special assessment groups (e.g., Endpoint Assessment Committees). It is equally critical that there be well-described, prospectively defined, evaluation criteria. Due to the nature and process of ECOG auditing of clinical sites instead of specific studies, the acknowledgement by CTEP that the auditing procedures employed were not adequate to assure compliance with GCP for specific trials, and the previously described confounding factors associated with the secondary endpoints of Study E4599, FDA requested that the Sponsor arrange for a limited audit of the objective response rate (ORR) data in Study E4599 by conducting an independent, blinded, adjudicated review of the complete series of radiology imaging assessments used for determining and confirming objective response from 21 subjects at three study sites. The Applicant provided the requested independent radiology audit of 20 of the 21 requested patients. Due to review cycle time constraints and the date the radiology audit was received by FDA, the Applicant requested that the PFS and ORR data not be included in the Package Insert. This reviewer notes that discrepancies were identified between the assessment of the source ORR data by ECOG and that of the independent radiology audit. In addition, the independent review identified concerns regarding image quality and incomplete film series.

6.1.6 Efficacy Conclusions

BV/CP demonstrated efficacy in a randomized, multi-center trial in prolonging the clinically meaningful duration of survival in patients with chemotherapy naïve, unresectable, recurrent or metastatic non-squamous NSCLC compared to patients who received CP alone. The secondary endpoints of PFS and ORR, although based on lower quality data, support the primary efficacy endpoint. The lack of a survival benefit in a subgroup representing 46% of the patients (female gender) enrolled on study is concerning. The Cox multivariate analysis suggests that a treatment effect of bevacizumab on prolongation of survival was still present in females despite the results of the simple univariate analysis. In addition to the multivariate analysis results, bevacizumab was also found to positively affect both PFS and ORR for females in favor of the BV/CP arm, although as previously described, these secondary endpoint are less reliable (see page 26) than the primary endpoint of duration of survival.

7 INTEGRATED REVIEW OF SAFETY

Clinical information from 488 patients who received Avastin in combination with carboplatin and paclitaxel in Study AVF0757g and Study E4599 was used to assess the overall toxicity profile of Avastin in the NSCLC population.

7.1 Methods and Findings

During the conduct of Study AVF0757g, a Phase 2 dose-finding and activity study, six subjects on the Avastin treatment arms experienced a life-threatening bleed that may have been caused by tumor-related hemorrhage from pulmonary tumors. The presumed pulmonary hemorrhage event was fatal in 4 cases. Genentech performed a review of the literature to estimate the rate for massive or major hemoptysis in this patient population and determined the rate to be near zero. An analysis performed by the Sponsor suggested that squamous histology and Avastin therapy were the most likely risk factors for fatal pulmonary bleeds. Based on the identification of a possible new safety signal involving massive pulmonary hemorrhage in patients treated with Avastin for squamous histology NSCLC, Study E4599 attempted to exclude patients with predominant squamous histology. An analysis of the adverse event data from Study AVF0757g did not suggest any additional new Avastin safety signals.

The following bulleted list highlights some of the limitations encountered during the safety review of Study E4599:

- Only Grade 4 or greater hematologic and Grade 3 or greater non-hematologic adverse events were to be recorded on the E4599 Toxicity Form.
- Adverse event onset dates were not recorded, but instead the reporting period during which the adverse events occurred was documented. ECOG and the other cooperative groups did not provide guidance as to the manner and frequency in which subjects were queried in regards to adverse events and instead each site was to follow their institution's process.
- The narratives are written using AdEERS derived verbiage abutted to Genentech verbiage without reconciliation of discrepancies or intent for readability.
- Narratives are not provided for any adverse events for patients in the CP treatment arm.
- The reason for treatment modification was not collected.
- Adverse events that led to the discontinuation of bevacizumab were not collected.
- The narratives for subjects coming off of study for toxicity reasons do not identify the toxicities responsible for discontinuation of protocol therapy.
    - The Sponsor states: *For narratives on events leading to study discontinuation, it may not be possible to identify the exact toxicity that led to the patient's discontinuation as this information was not collected. When the event leading to study discontinuation is not apparent, the information about adverse events that may have been associated with the discontinuation will be included in the narrative. In some cases, several adverse events may be reported..*
- The mechanism of expedited reporting of adverse events differed between treatment arms. Expedited reporting of adverse events occurring on the BV/CP arm was through AdEEERS while expedited reporting of adverse events on the CP arm was through MedWatch. The AdEERS reporting mechanism could include additional follow up queries by CTEP to clarify

and further characterize adverse events whereas the MedWatch reporting mechanism was a static process. The MedWatch expedited adverse event data for the CP arm was not provided for review. Comparisons of the incidence of adverse events between treatment arms that use expedited reporting cannot be performed.

- The study did not capture basic laboratory data such as electrolytes, urinalysis results or complete blood counts.

7.1.1 Deaths

FDA attempted to compare the frequencies of adverse events between treatment arms that occurred near the time of death. Study E4599 did not collect the onset date of adverse events but instead collected the reporting period during which the adverse event occurred. The reporting periods ranged from -348 to +392 days (as determined from the CRTs provided to FDA), however, the most frequent length of reporting period was 20 and 21 days. The "DEATH" data set and the "AE" data set were combined and the following formula was used to identify adverse events that occurred within 52 days of the "Adverse event reporting period begin date" and the date of death of subjects.

*If ((In Minutes (:DTHDT) - In Minutes (:AEREDT)) / (1440 * 60 * 60) < 30, 1, 0)*

The above approach will miss events that occurred close to death but involved protracted reporting periods. Notable differences in the adverse event spectrum that occurred within 52 days of death are presented in Table 10.

Table 10: Adverse Events within 52 Days of Death

	Number of patients with AE by treatment arm	
Adverse Event	**BV/CP** (53 subjects)	**CP** (54 subjects)
Hemoptysis	8	5
Pneumonitis/Pulmonary Infiltrates	7	5
Infection without Neutropenia	6	2
Leukocytes	5	1
Transfusion PRBC	3	0
Rash desquamation	3	0
Melena/GI bleeding	3	2
Hemoglobin	3	1
Proteinuria	2	0
CNS hemorrhage	2	0
Cerebrovascular Ischemia	2	0
Hemorrhage other	2	0
Hematemesis	2	0

Analysis of the spectrum of adverse events occurring near the time of death reveals that hemorrhagic events were more common in the BV/CP arm prior to death compared to the CP arm. The analysis also suggests that 1) *Infection without Neutropenia,* and 2) *Leukopenia,* were more common prior to death in the BV/CP arm compared to the CP arm.

Table 11 is reproduced from page 125 of CSR. In this table the Applicant reports the data as collected by the investigator in the CRF boxes provided, and did not integrate additional data found in the CRT or CRF that may have further clarified the cause of death or relatedness to

protocol treatment. For example, patient number 45027 was listed with the cause of death as unknown with the additional description of "found collapsed at home in a pool of blood" and patient number 45283 with the cause of death left as blank contained the additional description of COPD/Pneumonia, possible pulmonary hemorrhage caused by NSCLC.

Table 11: Sponsor's Analysis of Cause of Death

	CP (n=441)	BV/CP (n=427)	Total (n=868)
Total deaths	361 (81.9%)	329 (77.0%)	690 (79.5%)
Due to protocol treatment	1 (0.2%)	6 (1.4%)	7 (0.8%)
Due to this disease	326 (73.9%)	287 (67.2%)	613 (70.6%)
Due to other cause	15 (3.4%)	23 (5.4%)	38 (4.4%)
Unknown	16 (3.6%)	12 (2.8%)	28 (3.2%)
Not stated [a]	3 (0.7%)	1 (0.2%)	4 (0.5%)

CP=carboplatin/paclitaxel; BV/CP=bevacizumab+carboplatin/paclitaxel.
Note: Cause of death was collected from E4599 Treatment or Long-Term Follow-Up Forms.
[a] Patients who died and for whom a cause of death reason on the Long-Term Follow-Up or Treatment Form was not given are categorized as "not stated."

Line Listing 16.2/9 of the CSR was reviewed for deaths not due to progressive disease up to 30 days after the last dose of protocol therapy or deaths due to study drug more than 30 days after protocol therapy. The Sponsor included patients that died of "Constitutional Symptoms" in this line listing. "Constitutional Symptoms" appears to be a synonymous term for PD used by some investigators. The Applicant did not provide narratives for any subject in the CP treatment arm; therefore the CRFs were reviewed for all CP patients that died within these parameters. The narratives for patients on the BV/CP arm, and CRFs when necessary, were reviewed for the cause of death occurring in patients that died within the same parameters. It should be noted that the narratives and CRF data provided for review were lacking in detail and corroborative laboratory data. Table 12 summarizes the findings of this reviewer and the data as contained in the updated ADV (combined adverse event data source) provided by the Applicant as supplement 125085-85.004 on 07-JUL-06.

Table 12: Deaths not listed as PD up to 30 days after the last dose of protocol therapy or deaths due to study drug more than 30 days after protocol therapy

Treatment Arm	Deaths	Deaths hemorrhage	Total number of Grade 5 hemorrhage AEs listed throughout entire study from CRT	Pulmonary Hemorrhage	Total number of Grade 5 hemoptysis AEs listed throughout entire study from CRT	Progressive disease
CP	9 (not PD)	0	3	0	1	0
BV/CP	28 (not PD)	11	10	8	6	10

Table 13 is a case by case review of the 16.2/9 line listing of deaths occurring within 30 days of protocol therapy or related to investigational agent occurring greater than 30 days after protocol therapy. No new safety signals for bevacizumab were identified based on the review of this data.

Table 13: Case by Case Review of Deaths not listed as PD up to 30 days after the last dose of protocol therapy or deaths due to study drug more than 30 days after protocol therapy

Patient ID	Cause of Death from CRF	Cause of Death Reviewer assessment
CP Arm		
45217	Suicide	Agree
45235	unknown	Investigator states no autopsy performed
45246	SOB respiratory arrest in ER	No additional data provided
45381	F/N Pneumonia Sepsis	Agree
45488	Progressive disease	Agree, initially coded as grade 5 dyspnea
45455	Grade 5 depression	Hanging suicide
45592	Grade 5 cardiac left ventricular function	Disagree: Grade 5 cardiac ischemia, Grade 5 GI hemorrhage, Grade 5 hepatic failure, MedWatch form without attached narrative.
50021	Foaming from mouth	No additional data provided
50058	Grade 3 hypoxia changed to grade 5	No additional data provided
53006	Grade 5 renal failure (due to this disease)	Disagree: Medwatch report states patient admitted with UTI then pulmonary infection and positive yeast blood culture and hypotension. Neutropenic
BV/CP Arm	**Cause of Death from narrative**	
45012	Progressive disease constitutional symptoms and pneumonia	Agree: Progressive disease
45027	Grade 3 allergic reaction followed by grade 5 hemorrhage	Agree: Pulmonary hemorrhage
45043	Grade 5 constitutional symptoms	Progressive disease
45049	Grade 5 constitutional symptoms	Progressive disease
45096	Grade 5 constitutional symptoms	Agree: Grade 4 Creatinine (10.4) Renal stone Pneumonitis (lymphagiatic spread of tumor) hypoxia
45098	Grade 5 pneumonitis/pulmonary infitrates Grade 4 infection Neutropenia	Agree: F/N Septic Shock
45132	Grade 5 gastritis Grade 4 hematemesis Grade 4 GI bleed	Disagree: GI bleed gastric ulcer
45145	Grade 5 CNS ischemia	Agree: Infarct no hemorrhage
45154	Grade 5 infection without neutropenia and grade 4 perforated viscus	Disagree: Bowel perforation
45179	Grade 5 constitutional symptoms	Agree: Grade 4 infection non-neutropenic probably secondary to progressive disease.
45206	Grade 5 respiratory failure	Agree: Lower back pain, nausea and vomiting, possible aspiration, coded and died.
45209	Grade 5 pneumonitis	Agree: Pneumonia
45220	Grade 5 sudden death	Agree: Swollen leg, possible PE
45284	Grade 5 hemoptysis	Agree
45306	Grade 5 constitutional symptoms Grade 4 CNS hemorrhage Grade 4 MI	Agree: Hospice progressive disease complicated by CNS hemorrhage
45315	Grade 5 infection grade 4 neutropenia	Agree: F/N and Sepsis
45322	Grade 5 hemoptysis	Agree
45324	Grade 5 infection grade 4 neutropenia	Agree: F/N and Sepsis
45325	Grade 5 cardiac event	Agree: Witnessed arrest MI/arrhythmia?
45370	Grade 5 respiratory failure	Agree: Progressive disease Post obstructive pneumonia, fall

Patient ID	Cause of Death from CRF	Cause of Death Reviewer assessment
		with pneumothorax.
45379	Grade 5 pneumonia	Inadequate data provided
45383	Grade 5 constitutional symptoms	Agree: Received no bevacizumab—progressive disease after hypersensitivity to Paclitaxel grade4
45442	Grade 5 constitutional symptoms	Agree: Hospice progressive disease
45489	Grade 5 hemorrhage,Grade 3 melena/GI bleeding	Agree: Respiratory insufficiency associated with pulmonary bleeding
45524	Grade 5 hemoptysis	Agree
45528	Grade 5 infection	Agree: Pneumonia, sepsis, renal failure (not neutropenic)
45542	Grade 5 dyspnea	Disagree: ER death sudden worsening of dyspnea and hemoptysis (Pulmonary bleed)
45593	Grade 5 infection bilateral pneumonia	Agree: Gram negative pneumonia
47010	Grade 5 hemoptysis	Agree
50001	Grade 5 dyspnea, grade 4 proteinuria	Disagree: Progressive COPD may have been caused by pulmonary edema secondary to hypoalbuminemia.
50008	Grade 5 constitutional symptoms	Agree: Hospice progressive disease
50012	Grade 5 Cardiovascualr event	Agree: MI
50056	Grade 5 infection with neutropenia	Agree: F/N and Sepsis
50059	Grade 5 constitutional symptoms	Disagree: Severe bleeding from the face after a fall at home.
52006	Grade 5 constitutional symptoms	Agree: Pleural effusions hospice care progressive disease
53009	Grade 5 constitutional symptoms	Agree: PD
53011	Grade 5 hematemesis	Disagree: Coughing and copious bleeding from the mouth, 1 month prior with complaints of bloody sputum. "vomiting blood in commode" narrative states Grade 5 hemoptysis in one place, CRF says hematemesis.
53034	Grade 5 constitutional symptoms (sudden death) evening before no complains out with friends	Disagree: Dead in bed, no suggestion of PD
More than 30 days related to protocol therapy		
45095	Grade 5 cardiac infarction	Agree
45134	Grade 5 constitutional symptoms after grade 4 CNS infarct ischemia	Agree: Hospice care progressive disease
45256	Grade 5 hemoptysis	Agree: Narrative states event occurred > 30 days after last dose of bevacizumab

When only the data from the E4599 Toxicity Forms are used for analysis, 23 Grade 5 adverse events are identified in the BV/CP arm and none are coded as "Constitutional". When toxicity data from AdEERs is combined with the E4599 Toxicity Form a total of 42 Grade 5 adverse Events are identified. "Constitutional" adverse events are coded for 18 out of the 42 subjects and this most likely represents a synonym used for progressive disease. Four patients on the BV/CP arm coded as having a Grade 5 Constitutional AE were also coded with a second Grade 5 AE. There are 6 additional Grade 5 AEs identified from AdEERS that were not associated with a Grade 5 Constitutional AE and that were not identified in the E4599 Toxicity Form. This represents a 20% failure in reporting of Grade 5 AEs that are not related to PD based on the data sets provided for review. Two of these cases represented a differential reporting in the nature of the Grade 5 adverse event between the E4599 Toxicity Form and AdEERS. Table 14 represents the FDA identification of these cases while Table 15 is an excerpted table from page 127 of the CSR that represents the Applicant's presentation of the Grade 5 AE data. This reviewer notes that the Applicant included the term Grade 5 Gastritis in the table instead of interpreting the adverse event as a Grade 5 gastrointestinal hemorrhage.

Table 14: Differences in Grade 5 Adverse Events between the Toxicity Form and AdEERS

Patient ID	AE Reporting Source	AE	Grade	
45154	AdEERS	Infection w/o Neutropenia	5	Not identified in the E4599 Toxicity Form
45206	AdEERS	Pulmonary-Other	5	Not identified in the E4599 Toxicity Form
45209	AdEERS	Pneumonitis/Pulmonary Infiltrates	5	Not identified in the E4599 Toxicity Form
45379	AdEERS	Arrhythmia-other	5	
45379	AE	Pneumonitis/Pulmonary Infiltrates	5	Differentially reported between AdEERS and E4599 Toxicity Form
45528	AdEERS	Infection w/o Neutropenia	5	Not identified in the E4599 Toxicity Form
53011	AdEERS	Hemoptysis	5	
53011	AE	Hematemesis	5	Differentially reported between AdEERS and E4599 Toxicity Form

Table 15: Applicant Analysis of Grade 5 AE reporting Mechanism

Toxicity Category and Term	AE CRF Only		AdEERS and AE CRF
	CP (n = 441)	BV/CP (n = 427)	BV/CP (n = 427)
Any Grade 5 adverse event	9 (2.0%)	23 (5.4%)	42 (9.8%)
Constitutional symptoms			
Constitutional	1 (0.2%)	0 (0.0%)	18 (4.2%)
Hemorrhage			
Hemoptysis	1 (0.2%)	5 (1.2%)	6 (1.4%)
Hemorrhage—other	0 (0.0%)	2 (0.5%)	2 (0.5%)
Hematemesis	0 (0.0%)	1 (0.2%)	1 (0.2%)
CNS hemorrhage	1 (0.2%)	0 (0.0%)	0 (0.0%)
Hemorrhage with Grade 3 or 4 platelets	0 (0.0%)	0 (0.0%)	1 (0.2%)
Melena/GI bleeding	1 (0.2%)	0 (0.0%)	0 (0.0%)
Pulmonary			
Pneumonitis/pulmonary infiltrates	0 (0.0%)	2 (0.5%)	3 (0.7%)
Dyspnea	0 (0.0%)	2 (0.5%)	2 (0.5%)
Pulmonary—other	1 (0.2%)	0 (0.0%)	3 (0.7%)
ARDS	1 (0.2%)	0 (0.0%)	0 (0.0%)
Hypoxia	1 (0.2%)	0 (0.0%)	0 (0.0%)
Infection/febrile neutropenia			
Infection w/ Grade 3 or 4 neutropenia	0 (0.0%)	3 (0.7%)	3 (0.7%)
Infection without neutropenia	0 (0.0%)	1 (0.2%)	3 (0.7%)
Cardiovascular (general)			
Cardiac-ischemia	1 (0.2%)	3 (0.7%)	3 (0.7%)
Thrombosis/embolism	0 (0.0%)	1 (0.2%)	1 (0.2%)
Cardiac—other	0 (0.0%)	0 (0.0%)	1 (0.2%)
Neurology			
Cerebrovascular ischemia	0 (0.0%)	2 (0.5%)	2 (0.5%)
Depression	1 (0.2%)	0 (0.0%)	0 (0.0%)
Gastrointestinal			
Gastritis	0 (0.0%)	1 (0.2%)	1 (0.2%)
Cardiovascular (arrhythmia)			
Arrhythmia—other	0 (0.0%)	0 (0.0%)	1 (0.2%)
Hepatic			
Liver dysfunction/failure	1 (0.2%)	0 (0.0%)	0 (0.0%)
Renal/genitourinary			
Renal failure	1 (0.2%)	0 (0.0%)	0 (0.0%)

7.1.2 Other Serious Adverse Events

Hemorrhage Events and Pulmonary Hemorrhage

The Applicant performed an analysis of the AE data sets using the following terms as hemorrhage related adverse events: CNS hemorrhage, hematemesis, hematuria, hemoptysis, hemorrhage associated with surgery, melena/GI bleeding, rectal bleeding, hemorrhage—other, hemorrhage with or without Grade 3 or 4 thrombocytopenia, epistaxis, and vaginal bleeding.

Based on this analysis the Applicant identified 19 Grade 3–5 hemorrhagic events (4.4%) in the BV/CP arm and 5 in the CP arm (1.1%) as reported using the E4599 Adverse Event/Toxicity Form. The incidence of hemorrhagic events in the BV/CP arm was 4.7% (20/427 patients) when NCI AdEERS reports were included. FDA performed an analysis of the adverse event data set ADV using the following JMP formula script:

```
If((Contains( :AEPCTC, "HEM") | Contains( :AEPCTC, "BLEE") | Contains( :AEPCTC,
"EPIST")) > 0 & (Contains( :AEPCTC, "HEMOG") | Contains( :AEPCTC, "ISCHE")) < 1, 1, 0)
```

and confirmed the Applicant's identification of 20 Grade 3-5 hemorrhagic events. However, upon FDA review of the Narratives and CRFs for patients who were included in line listing 16.2/9 of the CSR and characterized as "Deaths not listed as PD up to 30 days after the last dose of protocol therapy or deaths due to study drug more than 30 days after protocol therapy" this reviewer identified highly suggestive data of additional hemorrhagic deaths (see Table 11).

FDA also identified all Grade 3-5 hemorrhagic events in the ADV data set and compared these events to all Grade 5 adverse events and observed that subject number 45132 was coded as having died from Grade 5 gastritis who also incurred a Grade 4 hematemesis event. This patient was not included in the Applicant's analysis of hemorrhagic deaths. The Applicant states that 8 of the hemorrhage events in the BV/CP arm (1.9%) were fatal. Of the 8 bevacizumab-treated patients who experienced a Grade 5 bleeding event, 6 experienced a Grade 5 event recorded as hemoptysis. This reviewer notes that the CRFs and narratives suggest that at least 11 fatal hemorrhagic events occurred on the BV/CP arm (2.6%) and that 8 of these events were suggestive of a pulmonary origin (1.9%).

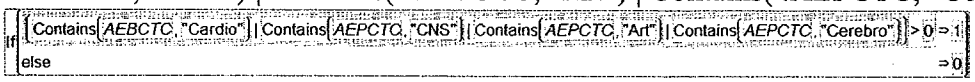
The Sponsor, ECOG, performed a review, conducted by the E4599 Study Chair and a thoracic oncology expert, of all hemorrhagic events and identified two additional cases that were thought to be of pulmonary origin. Based on this internal ECOG review, 7 Grade 5 hemorrhagic events of presumed pulmonary origin occurred. The Applicant describes this as an external independent review; however, the E4599 Study Chair conducted the review. The source data used for the expert review, autopsy reports and imaging data, was not provided in the supplement. The rationale for determination of the origin of the hemorrhage was deemed to be reasonable upon review.

Venous Thromboembolic Adverse Events

The CRFs were reviewed for 20 out of 24 subjects in the BV/CP arm that were coded as having incurred a Grade 3 or greater Venous Thromboembolic adverse event. The CRF for subject 45346 documents a left ventricular thrombus and not a venous thromboembolic adverse event. One out of the 20 selected cases did not have a CRF available for review. The BV/CP arm had an incidence rate for venous thromboembolic adverse events of 5.4% with one fatal case compared to 3.4% on the CP arm with no fatal cases reported.

Arteriothromboembolic Adverse Events

The Adverse Event data set was assessed for the classification scheme used for coding of thromboembolic and arteriothromboembolic events. The following formula was derived based on that assessment and used to broadly search the AEBCTC- and AEPCTC- columns for adverse events related to thrombosis/embolism: If((Contains(:AEBCTC, "Cardio") | Contains(:AEPCTC, "CNS") | Contains(:AEPCTC, "Art") | Contains(:AEPCTC, "Cerebro")) > 0, 1, 0)



The resulting table was assessed for events of an arterial thromboembolic nature and 19 patients (CP = 7 and BV/CP =12) were identified with an adverse event of Grade 3 or greater -Cardiac troponin, -Cardiac-ischemia, or -Cerebrovascular ischemia. This approach did not identify the previously miscoded case of a left ventricular (arterial) thrombus for subject 45346. This approach identified all the subjects for whom the sponsor provided CRFs for adverse events designated arterial thromboembolic events except the CRF under the section designated *Arterial Thromboembolic Events—Clinical Review.* This CRF (subject 47009) was reviewed and the *Expedited Adverse Event Report Form* has the statement that the treating physician said the patient might have had a small stroke accounting for the adverse event coded as confusion.

The incidence rate of arterial thromboembolic adverse events was 7/441 (1.6%) for the CP arm and 13/427 (3.0%) for the BV/CP arm. Five of 13 cases were fatal in the BV/CP arm compared to 1 of 7 in the CP arm. The increased incidence of arteriothromboembolic adverse events in subjects receiving bevacizumab is consistent with prior experience and is addressed in the current PI.

Gastrointestinal Perforation Related Adverse Events

Gastrointestinal perforation, intra-abdominal abscess, and fistula formation are infrequently observed but expected adverse events during bevacizumab therapy. The analysis of gastrointestinal perforation related adverse events in study E4599 is problematic for the following reasons:

1. There is no unique term or grade for gastrointestinal perforation or abscess events in NCI-CTC version 2.0 adverse event grading criteria system used in Study E4599.
2. Verbatim adverse event terms were not collected on the E4599 Toxicity Form.

The Sponsor performed a review of AdEERS and E4599 Toxicity form data in order to identify possible perforation related events. The Applicant's review was conducted as follows:

1. E4599 Toxicity Forms were searched for: "fistula", "gastrointestinal–other" and "infection/febrile neutropenia–other" and those with specific evidence of gastrointestinal perforation, intra-abdominal abscess, or fistula were identified.
2. NCI AdEERS reports were searched for specific evidence of gastrointestinal perforation, intra-abdominal abscess, or fistula formation.

An increased incidence of gastrointestinal perforation events was observed in the BV/CP arm 4/427 (0.9%) patients compared with the CP arm (no events reported). Two deaths occurred within 30 days of the event.

Neutropenia, Leucopenia, and Infections

CBC data was not collected for study E4599. Grade 4 neutropenia was required to be reported on the E4599 AE form. Analysis of the CRTs reveals that there was an increased incidence of Grade 4 neutropenia on the BV/CP arm 26.5% compared to 17.2% on the CP arm. The CRTs document

Grade 3 and 4 Leukocytes for 33 (7.7%) of patients on the BV/CP arm compared to 21 (4.8%) of patients on the CP arm. There were 38 (8.8%) patients on the BV/CP arm recorded as having incurred either *Infection with Grade 3 or 4 neutropenia* or *febrile neutropenia* compared to 17 (3.9%) patients on the CP arm. This reviewer attempted to identify all infection related adverse events that occurred within the first 6 cycles of therapy or within less than 24 weeks from the initiation of treatment, whether or not associated with neutropenia. The following adverse events were considered "infectious complications" by this reviewer: All Grade 3 or greater (pneumonitis/pulmonary infiltrates, infection without neutropenia, infection with grade 3 or 4 neutropenia, febrile neutropenia, catheter related infection, infection with an unknown ANC, infection-other, and wound infectious). When these events are considered, the BV/CP arm had 83 (19.4%) infectious complications compared to 38 (8.6%) on the CP arm throughout the entire study. Since patients were on treatment longer on the BV/CP arm, the same comparison was made during the first 6 cycles of treatment and the BV/CP arm had 58 (13.6%) infectious complications compared to 29 (6.6%) on the CP arm. The findings of increased infectious complications in patients receiving Avastin for NSCLC was also observed in the E3200 CRC study.

7.1.3 Dropouts and Other Significant Adverse Events

The number of patients who discontinued the study due to toxicity/side effects/complications prior to or at Cycle 6 was 60/429 (14.0%) in the BV/CP arm and 57/440 (13.0%) in the CP arm. The total number of patients that discontinued study due to toxicity on the BV/CP arm was 73. The E4599 study did not identify the toxicities responsible for discontinuation of protocol therapy due to toxicity, therefore accurate dissection of dropouts secondary to toxicity is not possible. The Applicant states that the event that led to discontinuation of study treatment was not required to be recorded on the E4599 Treatment Form. When the event that led to discontinuation was not apparent, events that may have been associated with discontinuation were identified to the extent possible using available data; in some cases, several events may have been reported.

The applicant generated a 62 page line listing "Listing 16.2/10" in the CSR showing all adverse events that occurred during a reporting period that began 30 days prior to study discontinuation or ended 30 days after study discontinuation for patients who discontinued due to an adverse event, side effects, or complications as reported on ECOG Form 1783 or in NCI AdEERS. The Applicant-provided line listing was reviewed. In order to identify a possible differential safety signal between the treatment arms relating to toxicity that might have been responsible for patient discontinuation, FDA performed the following analysis:

> The ADV data set was sorted based on the STDSRS variable data column (reason for study discontinuation) and all rows containing *Death on Study, Disease Progression, Treatment Completed per Protocol* and *Blank* were deleted while *Other, Alternative Therapy, Other Complicating Disease, Patient Withdrawal or Refusal after beginning Protocol Therapy, Toxicity Side Effects/Complications* were compiled. All collected adverse events were identified where the STDSDT variable data column (study discontinuation date) occurred on or after the AERBDT (adverse event reporting period begin date) or on or before the AEREDT (adverse event reporting period end date).

See Appendix 2 for a complete listing of the adverse events identified. This analysis is confounded by the variable reporting period durations that were used during the study. Table 16 represents a selected subset of adverse events that appeared quantitatively or qualitatively

different between treatment arms. This analysis did not identify any safety signals that are not already described in the package insert.

Table 16: Adverse Events Associated with Study Discontinuation

Adverse Event	Number of AE reported (%)	
	BV/CP (n=116)	CP (n=94)
CARDIAC TROPONIN I CARDIAC-ISCHEMIA	2 (1.7%)	1 (1.1%)
CEREBROVASCULAR ISCHEMIA	2 (1.7%)	1 (1.1%)
FISTULA-ESOPHAGEAL FISTULA-RECTAL/ANAL	2 (1.7%)	0
HEMMORRHAGE HEMATURIA EPISTAXIS MELENA/GI BLEEDING VAGINAL BLEEDING HEMOPTYSIS CNS HEMORRHAGE	13 (11.2%)	1 (1.1%)
HEMOGLOBIN	5 (4.3%)	1 (1.1%)
OSTEONECROSIS	1 (0.9%)	0
PNEUMOTHORAX	1 (0.9%)	0
PULMONARY FIBROSIS	1 (0.9%)	0
HEADACHE	6 (5.2%)	0
HYPERTENSION	6 (5.2%)	1 (1.1%)
HYPOTENSION	7 (6.0%)	3 (3.2%)
PROTEINURIA	7 (6.0%)	1 (1.1%)
DIARRHEA	8 (6.9%)	2 (2.1%)
THROMBOSIS/EMBOLISM	12 (10.3%)	5 (5.3%)
NEUROPATHY-SENSORY	15 (13%)	21 (22%)

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7.1.5 Common Adverse Events

Table 17 is excerpted from the CSR. Each of the adverse event incidence rates in this table was compared to the data in the adverse event data set. No discrepancies were identified between the table and the data as contained in the adverse event data set provided with this submission.

Table 17

E4599: Adverse Events Reported in the Adverse Event/Toxicity Form and/or in NCI AdEERS with a ≥2% Difference in Incidence between Arms: Treated Patients

Toxicity Category Term	AE CRF Only		AdEERS and AE CRF
	CP (n=441)	BV/CP (n=427)	BV/CP (n=427)
Blood/bone marrow			
Neutropenia	76 (17.2%)	112 (26.2%)	113 (26.5%)
Pulmonary			
Pneumonitis/pulmonary infiltrates	11 (2.5%)	15 (3.5%)	21 (4.9%)
Pain			
Headache	2 (0.5%)	13 (3.0%)	13 (3.0%)
Constitutional symptoms			
Fatigue	57 (12.9%)	67 (15.7%)	67 (15.7%)
Constitutional	1 (0.2%)	0 (0.0%)	19 (4.4%)
Cardiovascular (general)			
Hypertension	3 (0.7%)	32 (7.5%)	33 (7.7%)
Thrombosis/embolism	14 (3.2%)	20 (4.7%)	24 (5.6%)
Infection/febrile neutropenia			
Infection w/o neutropenia	12 (2.7%)	22 (5.2%)	30 (7.0%)
Febrile neutropenia	8 (1.8%)	19 (4.4%)	23 (5.4%)
Infection w/ Grade 3 or 4 neutropenia	9 (2.0%)	12 (2.8%)	19 (4.4%)
Metabolic/laboratory			
Hyponatremia	5 (1.1%)	15 (3.5%)	16 (3.7%)
Renal/genitourinary			
Proteinuria	0 (0.0%)	13 (3.0%)	13 (3.0%)

BV/CP=bevacizumab+carboplatin/paclitaxel; CP=carboplatin/paclitaxel.

Common Adverse Events of Particular Interest

Proteinuria

The Study Parameters of the protocol document that urine dipstick for protein was to be performed for the first 6 cycles for both treatment arms and thereafter for the BV/CP arm prior to bevacizumab administration. Urine Dipstick measurements were missing on at least one occasion for 226 patients on the CP treatment arm compared to 164 patients on the BV/CP arm. This suggests that there may have been an ascertainment bias in monitoring for proteinuria. There were 13 (3.0%) Grade 3 or greater proteinuria adverse events on the BV/CP arm compared to zero events on the CP arm. During review of the proteinuria data additional concerns regarding either the conduct or recording of the study were identified. The following section is excerpted from the protocol:

> 5.321 **Proteinuria**
>
> A dipstick urinalysis is required prior to each bevacizumab infusion. Trace + proteinuria on dipstick urinalysis should not be considered a positive result but should be repeated. If repeat confirms trace + proteinuria, no additional evaluation is necessary and the patient should continue therapy as planned. At initial documentation of significant proteinuria (> 1+ by urine dipstick) patients should undergo additional evaluation including the following:
>
> • 24-hour urine collection for total protein and creatinine clearance
> • Urine protein/creatinine ratio
> • Urinary protein electrophoresis

• Microscopic examination of fresh urine

If the 24-hour urine collection confirms proteinuria < 2000 mg within 24 hours, the patient may continue bevacizumab treatment as planned. A 24-hour urine collection for total protein and creatinine clearance must be performed prior to each subsequent cycle of therapy (every 3 weeks) to monitor the degree of proteinuria until it has decreased to < 500 mg/24 hours.

Patients who develop > 2000 mg proteinuria within 24 hours should continue treatment with paclitaxel and carboplatin and should not receive additional doses of bevacizumab until the proteinuria improves to < 2000 mg within 24 hours. Patient can then resume treatment at the same dose and schedule. The 24-hour urine collection should be repeated at the start of each subsequent 3-week cycle of therapy to monitor the degree of proteinuria.

The "Urine" data set documents 66 patients on the BV/CP treatment arm with 2^+ or greater urine dipstick measurements, however, only 3 of the 66 patients have a 24 hour urine protein measurement recorded. The Applicant states that ECOG did not collect 24-hour urine protein measurements except at baseline and the three 24-hour measurements documented are baseline values that are coincident with a 1^+ or greater dipstick value. Twenty-seven patients were administered bevacizumab on the same day that a 2^+ or greater urine dipstick measurement was recorded. The applicant states the following:

> The determination of 24-hour urine protein levels post-baseline was recommended in cases of significant proteinuria (≥ 1+ by urine dipstick) to guide treatment decisions with respect to interruption or discontinuation of bevacizumab. Data was not collected on the E4599 Treatment Form (Form No. 1705) for determination of post-baseline 24-hour urine protein levels (UPC) on the occasion of a ≥ 1+ urine dipstick prior to bevacizumab infusion. Therefore, the E4599 Protocol was adhered to with respect to 24-hour urine protein measurements. The National Cancer Institute (NCI) was responsible for conduct of routine audits for protocol compliance with respect to dose modification as assessed at selected sites.

This reviewer understands the protocol to read that a 24 hour urine protein measurement was to be obtained for dipstick values greater than 1^+ and therefore the protocol could not have been adhered to if the patient was administered bevacizumab on the same day as a greater than 1^+ urine dipstick measurement was recorded. This reviewer also notes that the study was initiated prior to approval of Avastin and that there was considerable concern at that time regarding the extent of bevacizumab-induced renal toxicity. This reviewer also notes that there was no real-time monitoring of the E4599 study and instead CTEP "auditing" procedures were employed.

Hypertension

Grade 3 hypertension was documented in 33 (7.7%) patients in the BV/CP arm compared to 3 (0.7%) on the CP arm. During the first 6 cycles of treatment, 23 patients on the BV/CP arm were noted to have Grade 3 or greater hypertension on 41 different visits with a mean number of hypertensive visits of 1.78 (standard deviation 1.59) compared to 3 patients and 4 visits for the control arm. During the first 6 cycles of treatment, 163 (38.2%) patients on the BV/CP arm were documented as having either a diastolic blood pressure greater than 100 or a systolic blood pressure greater than 150 compared to 120 (27.2%) of patients on the CP arm. The mean, standard deviation, and median for the number of blood pressure measurements obtained per patient during the first 6 cycles of treatment did not suggest a clinically relevant ascertainment bias for this variable (BV/CP Mean 4.77, Std 1.78, Median 6.0; CP Mean 4.34, Std 1.80, Median 5.0). The PI adequately describes the known hypertensive effects of Avastin.

Hyponatremia

Study E4599 did not collect laboratory data. This reviewer analyzed the electrolyte data from Study AVF0757g and did not find any meaningful differences in the mean, standard deviation, and median of serum sodium levels between treatment arms. Study E4599 revealed an increased incidence of Grade 3 or greater hyponatremia in the BV/CP arm 16 (3.7%) compared to the CP arm 5 (1.1%). The CRFs from the 16 cases of hyponatremia on the BV/CP arm were reviewed in an attempt to further elucidate the etiology of the hyponatremia. Adverse event onset dates were not collected in Study E4599 and instead a "reporting period" during which the event occurred was recorded. This failing of the study limits the ability to temporally associate adverse events with each other. A number of the cases of hyponatremia were probably associated with episodes of emesis, diarrhea, and pneumonia. In addition, 3 cases of hyponatremia were noted to occur in reporting periods subsequent to the first recording of a hypertensive adverse event in a recent prior reporting period. One CRF notes that hydrochlorathiazide may have been a contributing factor. Since Study E4599 did not record concomitant medications, the ability to discern bevacizumab related toxicities from toxicities induced by medications to treat known bevacizumab toxicities is severely limited. Based on the data in Study E4599, Study AVF0757g, and the previous FDA reviewed bevacizumab studies, no clear correlation between bevacizumab treatment and hyponatremia is evident at this time, however, the descriptive data regarding hyponatremia should be incorporated into the PI.

7.1.5.1 Eliciting adverse events data in the development program

ECOG and the other cooperatives did not provide any guidance as to the manner and frequency in which subjects were queried in regards to adverse events and instead each site was to follow their institution's process.

The study also did not capture basic laboratory data such as electrolytes, urinalysis and 24-hour urine protein measurements, or complete blood counts.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event data set provided uses NCI-CTC version 2 terminology for Adverse Event description including the NCI-CTC Adverse event Category and Organ System description. This reviewer finds the lack of granularity in the NCI-CTC Adverse Event dictionary to be a limiting factor when attempting to characterize various adverse events.

7.1.5.4 Common adverse event tables

Table 18 is an FDA analysis of the adverse event data and includes events documented on the E4599 Toxicity Form and in AdEERS. All Grade 3-5 non-hematologic and Grade 4-5 hematalogic events are represented. The highlighted rows correspond to incidence rates that differed by $\geq 2\%$. This analysis is similar to the Sponsor's analysis for events that occurred with greater than a 2% difference in incidence between treatment arms as seen in Table 17.

Table 18: Adverse events occurring at greater than 2 percent in either treatment arm

ADVERSE EVENT	CP n (441)	%	BV/CP n (427)	%	BV/CP% - CP%
ABDOMINAL PAIN	6	1.36	14	3.28	1.92
ALLERGIC REACTION	13	2.95	17	3.98	1.03
ANOREXIA	17	3.85	24	5.62	1.77
ARTHRALGIA	16	3.63	18	4.22	0.59
BONE PAIN	18	4.08	18	4.22	0.13
CHEST PAIN	4	0.91	9	2.11	1.20
CONFUSION	10	2.27	11	2.58	0.31
CONSTIPATION	15	3.40	13	3.04	-0.36
CONSTITUTIONAL*	1	0.23	19	4.45	4.22
COUGH	8	1.81	10	2.34	0.53
DEHYDRATION	18	4.08	23	5.39	1.30
DIARRHEA	9	2.04	15	3.51	1.47
DIZZINESS/ LIGHTHEADEDNESS	8	1.81	14	3.28	1.46
DYSPNEA	66	14.97	57	13.35	-1.62
FATIGUE*	57	12.93	67	15.69	2.77
FEBRILE NEUTROPENIA*	8	1.81	23	5.39	3.57
HEADACHE*	2	0.45	13	3.04	2.59
HEMOPTYSIS	2	0.45	9	2.11	1.65
HYPERGLYCEMIA	17	3.85	17	3.98	0.13
HYPERTENSION*	3	0.68	33	7.73	7.05
HYPONATREMIA*	5	1.13	16	3.75	2.61
HYPOTENSION	11	2.49	14	3.28	0.78
HYPOXIA	15	3.40	14	3.28	-0.12
INFECTION W/ GRADE 3 OR 4 NEUTROPENIA*	9	2.04	19	4.45	2.41
INFECTION W/O NEUTROPENIA*	12	2.72	30	7.03	4.30
LEUKOCYTES	11	2.49	19	4.45	1.96
MUSCLE WEAKNESS	15	3.40	17	3.98	0.58
MYALGIA	21	4.76	17	3.98	-0.78
NAUSEA	25	5.67	27	6.32	0.65
NEUROPATHY-SENSORY	48	10.88	39	9.13	-1.75
NEUTROPHILS*	76	17.23	113	26.46	9.23
PNEUMONITIS/PULMONARY INFILTRATES*	11	2.49	21	4.92	2.42
PROTEINURIA*	0	0.00	13	3.04	3.04
RASH/DESQUAMATION	4	0.91	10	2.34	1.43
SYNCOPE	9	2.04	8	1.87	-0.17
THROMBOSIS/EMBOLISM*	14	3.17	24	5.62	2.45
TRANSFUSION: PRBCS	2	0.45	10	2.34	1.89
VOMITING	20	4.54	25	5.85	1.32

*Adverse event incidence rates that differ by ≥ 2%

7.1.7 Laboratory Findings

Laboratory data (including complete blood counts and serum chemistries) were not required to be collected on CRFs during the conduct of study E4599.

7.1.8 Vital Signs

Vital sign data was reviewed. An increased incidence of elevated systolic blood pressure was observed in the BV/CP arm compared to the CP arm. Hypertension, a known toxicity of bevacizumab, is adequately described in the PI.

7.1.9 Electrocardiograms (ECGs)

The current Warnings Section of the PI describes congestive heart failure as a possible complication of bevacizumab treatment. No ECG data was collected during the conduct of study E4599. The incidence of congestive heart failure was 0.7% on the BV/CP arm compared to 0.5% on the CP arm.

7.1.10 Immunogenicity

Immunogenicity studies were not performed during the conduct of study E4599.

7.1.11 Human Carcinogenicity

Human carcinogenicity studies were not conducted during study E4599. The carcinogenicity of bevacizumab (a humanized monoclonal antibody) cannot be adequately assessed in rat models secondary to the immunogenicity of the product. Homolog carcinogenicity studies were not conducted during the development of bevacizumab since a plausible biological mechanism for bevacizumab induction or promotion of neoplasia was not readily apparent. No post-marketing safety signals suggesting an increase incidence of secondary malignancies has been observed with Avastin use.

7.1.12 Special Safety Studies

No Special Safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no known withdrawal phenomena or abuse potential associated with bevacizumab.

7.1.14 Human Reproduction and Pregnancy Data

No additional reproduction studies were conducted or data collected during the E4599 study. The current package insert contains the following information regarding Pregnancy:

> AVASTIN has been shown to be teratogenic in rabbits when administered in doses that approximate the recommended human dose on a mg/kg basis. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions, and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested.
>
> Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of AVASTIN is likely to result in adverse effects on pregnancy. There are no adequate and well-controlled studies in pregnant women. AVASTIN should be used during

pregnancy or in any woman not employing adequate contraception only if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of AVASTIN to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving AVASTIN, she should be apprised of the potential hazard to the fetus and/or the potential risk of loss of pregnancy. Patients who discontinue AVASTIN should also be counseled concerning the prolonged exposure following discontinuation of therapy (half-life of approximately 20 days) and the possible effects of AVASTIN on fetal development.

7.1.15 Assessment of Effect on Growth

Additional studies on growth effects were not conducted during this study. Please see the current PI Precautions Section Pediatric Use for preclinical information on physeal dysplasia.

7.1.16 Overdose Experience

No overdose experience was reported in the E4599 CSR. Patient 45586 received 20.25 mg/kg of bevacizumab on cycle 8. No adverse events are documented for this patient in the CRTs and no CRF is available for review. Patient 53046 received 22.14 mg/kg of bevacizumab on cycle 3. No adverse events are documented for this patient in the CRTs and no CRF is available for review.

7.1.17 Postmarketing Experience

The safety concerns regarding Avastin use obtained from postmarketing experience are adequately described in the current Avastin Package Insert/Prescribing Information.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

A total of 427 patients in the BV/CP arm, and 441 patients in the CP arm received at least one component of protocol therapy. The sponsor states that, except for bevacizumab, data were not available for exposure to individual components of protocol therapy. The CRTs reveal that 11 subjects were not documented as having received bevacizumab. Five of the subjects with no CRT documentation of bevacizumab administration were enrolled through the Expanded Participation Program and collection of this information was not required. Based on review of the CRF data for the remaining 6 patients, four patients did not receive any bevacizumab, one patient's complete set of Treatment Forms were missing, and one patient's CRF was not available for review. The median number of cycles of bevacizumab treatment in the BV/CP arm was 8 and the mean dose of bevacizumab administered was 15.1 mg/kg with a standard deviation of 3.53.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Secondary data sources were not provided by the sponsor or utilized from other sources for this efficacy supplement.

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience of this study was adequate to conclude that no new major-safety concerns are likely in this subject population other than the risk of fatal pulmonary hemorrhage already described in the Package Insert/Prescribing Information. However, the lack of collection of adverse event onset dates, laboratory data, and concomitant medications limits the safety information that can be discerned from the study.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing data captured during this study was not adequate.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of safety data was inadequate.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most serious design flaw of this study was the collection of adverse event data by reporting periods (of varied duration) instead of adverse event -onset and -ending dates. The fact that the sponsor was not able or unwilling to provided narratives for control subjects, and the quality of the narratives provided (gross inconsistencies between narrative and CRF data) severely limits the interpretation of the narrative data. The study data suggest that the incidence of hyponatremia, neutropenia, febrile neutropenia, and non-neutropenic infections may be increased in the BV/CP arm compared to the control CP arm. Some of the hyponatremia events may have been secondary to medications initiated to treat hypertension induced by bevacizumab treatment; however, this cannot be adequately assessed due to the nature of data collection in Study E4599.

The nature and incidence of the following adverse events identified in the current study appears to be consistent with the information already contained in the Avastin PI/Prescribing Information: Intestinal perforation, hemorrhage, arterial thromboembolic events, hypertension, and proteinuria. The AVF0757g and E4599 study data strongly suggest that patients with squamous histology NSCLC or with NSCLC and a history of prior gross hemoptysis ($\geq$ ½ tsp) are at increased risk for life threatening pulmonary hemorrhage.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Comparisons of the results from Study E4599 with previous Genentech or ECOG sponsored studies using bevacizumab was not considered useful because of the respective differences in the

subject populations under study, the chemotherapy regimens employed, and the difference in extent of prior therapies received by patients.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Two previous studies conducted by the Sponsor (AVF0780g and AVF2106g) suggested a bevacizumab dose related increase in the incidence of hypertension from 5 mg/kg to 10 mg/kg every 2 weeks. Study AVF0757g employed two doses of bevacizumab, either 7.5 mg/kg or 15 mg/kg every three weeks. Although this was a small study, there was some suggestion that an increased dose of bevacizumab may be associated with a higher incidence rate of hypertension as can be seen below.

	Control		7.5 mg/kg		15 mg/kg	
	All Events	Grade 3/4	All Events	Grade 3/4	All Events	Grade 3/4
Cardiovascular						
Hypertension	**1 (3.1%)**	**1**	**5 (15.6%)**	**0**	**6 (17.6%)**	**2**

Explorations for drug-demographic interactions

The following tables are reproduced from the CSR. Comparisons between subgroups should be interpreted cautiously given the relatively small numbers of patients, potential imbalances in patient characteristics between treatment arms within the subgroups, and differential time on therapy in the study arms. There was the suggestion of an increased relative risk of *proteinuria* and *leucopenia* in patients over 65 years of age who received bevacizumab compared to patients younger than 65 years of age. The data suggest that females receiving bevacizumab had an increased relative risk for *infection without neutropenia* and *abdominal pain* compared to males. The total number of non-white patients and the number of non-white patients with specific adverse events makes comparisons unlikely to be useful for even exploratory purposes, however, the data is provided in tabular format for descriptive purposes.

E4599: Adverse Events by Age, with Incidence Rates that Differ between Age Groups 40–64 Years and ≥ 65 Years by ≥4%: Treated Patients

Toxicity Category Term [a]	Age Category					
	< 40 years (n = 13)		40–64 years (n = 479)		≥ 65–years (n = 376)	
	CP (n=4)	BV/CP (n=9)	CP (n=243)	BV/CP (n=236)	CP (n=194)	BV/CP (n=182)
Blood/bone marrow						
Neutropenia	0 (0.0%)	2 (22.2%)	34 (14.0%)	46 (19.5%)	42 (21.6%)	64 (35.2%)
Leukopenia	0 (0.0%)	1 (11.1%)	4 (1.6%)	3 (1.3%)	7 (3.6%)	14 (7.7%)
Constitutional symptoms						
Fatigue	0 (0.0%)	2 (22.2%)	29 (11.9%)	30 (12.7%)	28 (14.4%)	35 (19.2%)
Cardiovascular (general)						
Hypertension	0 (0.0%)	1 (11.1%)	2 (0.8%)	18 (7.6%)	1 (0.5%)	13 (7.1%)
Renal/genitourinary						
Proteinuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.7%)	0 (0.0%)	9 (4.9%)

E4599: Adverse Events by Sex with Incidence Rates that Differ between Groups by ≥4%: Treated Patients

	Males (n=473)		Females (n=395)	
NCI-CTC Toxicity Category Term	CP (n=258)	BV/CP (n=215)	CP (n=183)	BV/CP (n=212)
Blood/bone marrow				
Neutrophils	45 (17.4%)	59 (27.4%)	31 (16.9%)	53 (25.0%)
Constitutional symptoms				
Fatigue	34 (13.2%)	29 (13.5%)	23 (12.6%)	38 (17.9%)
Cardiovascular (general)				
Hypertension	1 (0.4%)	9 (4.2%)	2 (1.1%)	23 (10.8%)
Infection/febrile neutropenia				
Infection without neutropenia	10 (3.9%)	11 (5.1%)	2 (1.1%)	11 (5.2%)
Pain				
Abdominal pain	4 (1.6%)	2 (0.9%)	2 (1.1%)	11 (5.2%)

E4599: Adverse Events by Race with Incidence Rates That Differ between Groups by ≥4%: Treated Patients

NCI-CTC Toxicity Category Term [a]	White (n = 744)		Non-White (n = 124)	
	CP (n = 385)	BV/CP (n = 359)	CP (n = 56)	BV/CP (n = 68)
Blood/Bone Marrow				
Neutropenia	64 (16.6%)	93 (25.9%)	12 (21.4%)	19 (27.9%)
Pulmonary				
Dyspnea	59 (15.3%)	51 (14.2%)	7 (12.5%)	4 (5.9%)
Neurology				
Neuropathy—sensory	41 (10.6%)	34 (9.5%)	7 (12.5%)	5 (7.4%)
Neuropathy—motor	4 (1.0%)	5 (1.4%)	4 (7.1%)	1 (1.5%)
Cerebrovascular ischemia	0 (0.0%)	5 (1.4%)	3 (5.4%)	0 (0.0%)
Cardiovascular (general)				
Hypertension	2 (0.5%)	22 (6.1%)	1 (1.8%)	10 (14.7%)
Thrombosis/embolism	13 (3.4%)	16 (4.5%)	1 (1.8%)	4 (5.9%)
Pain				
Arthralgia	15 (3.9%)	13 (3.6%)	1 (1.8%)	4 (5.9%)
Abdominal pain	6 (1.6%)	8 (2.2%)	0 (0.0%)	5 (7.4%)
Headache	2 (0.5%)	9 (2.5%)	0 (0.0%)	4 (5.9%)
Gastrointestinal				
Nausea	21 (5.5%)	25 (7.0%)	4 (7.1%)	1 (1.5%)
Infection/febrile neutropenia				
Febrile neutropenia	8 (2.1%)	13 (3.6%)	0 (0.0%)	6 (8.8%)
Infection w/Grade 3 and 4 neutropenia	5 (1.3%)	11 (3.1%)	4 (7.1%)	1 (1.5%)
Metabolic/laboratory				
Hyperglycemia	13 (3.4%)	16 (4.5%)	4 (7.1%)	1 (1.5%)
Allergy/immunology				
Allergic reaction	8 (2.1%)	14 (3.9%)	5 (8.9%)	3 (4.4%)
Renal/genitourinary				
Proteinuria	0 (0.0%)	10 (2.8%)	0 (0.0%)	3 (4.4%)

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosage of bevacizumab evaluated in Study E4599 was 15 mg/kg administered as an IV over 90 minutes that could be reduced to 30 minutes as tolerated with subsequent infusions. This differs from the current label recommendation of 5 to 10 mg/kg given once every 14 days as an IV infusion.

8.2 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted.

8.3 Special Populations

The efficacy supplement submitted contained no specific studies to evaluate dosing based on race, gender, age or major organ impairment. Subgroup analyses based on race, gender and age, were conducted for Study E4599 and the results are presented in section 6.1.4.3 and 7.4.2.3. No safety data from Study E4599 suggested that dosing should be modified based on demographic characteristics, however, as previously discussed; the lack of a survival benefit in females is still unexplained.

8.4 Pediatrics

A "Phase I Study of Bevacizumab in Refractory Solid Tumors" conducted by the Children's Oncology Group to characterize the pharmacokinetics of bevacizumab in pediatric patients is an ongoing post-marketing commitment for Avastin. Patient accrual has been completed and the final study report is to be submitted to FDA by the 31 December 2006.

A waiver for the requirement of additional pediatric studies will be granted in association with this supplement, given that NSCLC rarely occurs in patients less than 18 years of age.

8.6 Literature Review

The applicant conducted a review of the literature and submitted an extensive reference section for the sBLA. The FDA conducted selected searches of the literature for specific issues pertaining to this supplement and reviewed the Applicant's submitted references.

8.7 Postmarketing Risk Management Plan

Based on the safety review findings, no postmarketing risk management plan is necessary for Avastin.

9 OVERALL ASSESSMENT

9.1 Conclusions

The addition of bevacizumab to carboplatin and paclitaxel provided a statistically significant and clinically meaningful improvement in overall survival compared to carboplatin and paclitaxel alone in patients who had unresectable or metastatic, non-squamous NSCLC. The secondary endpoint of PFS supported the improvement in overall survival. The safety profile of bevacizumab, as demonstrated in this study, did not reveal new, clinically-significant safety signals or adversely impact on subjects' quality of life. Subset analyses suggest that females and patients with greater than 5% body weight loss at study entry received less benefit from the addition of bevacizumab to carbolplatin and paclitaxel chemotherapy.

9.2 Recommendation on Regulatory Action

This reviewer recommends approval of the BLA efficacy supplement STN 125085.85 for the use of Avastin in combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable or metastatic non-squamous NSCLC. Modifications to the Applicant proposed labeling and additional postmarketing commitments will be required prior to approval.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No postmarketing risk management plan is required.

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

It is recommended that the Sponsor agree to the following PMCs:

- To submit an efficacy supplement containing the final study report, including summary analyses, primary datasets and appropriate revised labeling describing the effects of overall survival in the entire population and by gender and age, from the Hoffman-LaRoche-sponsored study, BO17704, "A Randomized, Double-Blind, Multicenter Phase 3 Study of Bevacizumab in Combination with Cisplatin and Gemcitabine Versus Placebo, Cisplatin and Gemcitabine in Patients with Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer Who Have Not Received Prior Chemotherapy". A copy of the protocol was submitted to BB-IND 7023 on February 13, 2006 and patient accrual was completed by August 31, 2006. The study will be completed by June 20, 2008, and the

supplement containing the final study report and revised labeling will be submitted by December 31, 2008.

- To submit as a supplement a final safety report, and revised labeling, describing the adverse event profile of Avastin administered to patients with previously treated central nervous system (CNS) metastases. The supplement will contain information on an integrated safety population of at least 50 patients with previously treated CNS metastases enrolled on studies AVF3752g or AVF3671g, to include summary safety analyses, primary datasets with demographic, treatment and safety information, case report forms for all deaths and dropouts, and narrative summaries for all patients with serious adverse events in either study. For those patients enrolled in Study AVF3752g, the supplement will contain information on the number and size of brain metastases. Protocol AVF3752g was submitted to BB-IND 7023 on November 30, 2005. Protocol AVF3671g will be submitted by November 30, 2006, accrual of the minimum number of 50 patients will occur by January 31, 2008 and the supplement containing the final safety report and revised labeling will be submitted by March 31, 2008.
- To submit a safety update on an annual basis containing safety information summarizing and characterizing NCI CTC ver. 3 Grade 2-5 adverse events involving the CNS from the following three placebo-controlled, randomized studies: OSI3364g (non-small cell lung cancer) and AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). For studies which have not been completed, the annual update of information will be generated by an independent unblinded data coordinating center that will not share information with any individual involved in the design, conduct or analysis of the trials. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005 and protocol AVF3995g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 30, 2006, and the annual safety updates will be submitted by Dec. 31, 2007, Dec. 31, 2008, and Dec, 31, 2009.
- To submit as a supplement a final safety report containing revised labeling, as applicable, based on data from a minimum of 100 patients with CNS metastases (roughly half of whom were randomized to Bevacizumab plus additional anti-cancer agents) enrolled in studies OSI3364g (non-small cell lung cancer), AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). The supplement will include summary analyses and primary datasets, including the number and size of CNS metastases for each patient. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005 and protocol AVF3993g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 20, 2006, a statistical analysis plan for integrated summary analyses will be submitted by June 30, 2007, and the supplement containing the final safety report and revised labeling will be submitted by December 31, 2010.
- To conduct a sub-study to address the impact of Bevacizumab on the QT interval. This sub-study will be added to three planned or ongoing randomized placebo-controlled studies in breast cancer, ovarian cancer, and extensive stage small cell lung cancer. The sub-study will collect replicate ECG measurements at baseline and at various time points correlating with drug exposure. Approximately 60 Bevacizumab-treated patients and 60 controls will be evaluated in this sub-study. A detailed protocol for this sub-study will be submitted by January 31, 2007. The sub-study will be initiated by June 30, 2007 and will

be completed by June 30, 2010. A report based on this study will be submitted by December 31, 2010.

9.4 Labeling Review

Multiple labeling meetings were held with the Applicant to negotiate acceptable Package Insert language.

Please see section 10.2 for the agreed upon complete Package Insert language.

The following points highlight the changes made to the Package Insert:

b(4)

- The Dosage and Administration section was revised to reflect the dose administered in Study E4599.

9.5 Comments to Applicant

No additional comments to the applicant were provided.

10 APPENDICES

Appendix 1

Protocol Amendments and changes to the SAP

The protocol was amended nine times. Substantive changes are briefly described below.

Amendment 1, August 8, 2002:

- MRIs were added to the eligibility section.
- The time frame for required lab values was changed from 4 weeks to one week
- The time frame for renal function tests was changed from 4 weeks to one week, and the protocol allowed for urinalysis.
- A history of gross hemoptysis was added as an exclusion criterion.
- The NCI required infusion instructions for bevacizumab were added.
- AdEERS reporting requirements were modified.
- EKG was removed as a required test.

Amendment 2, January 29, 2003:

- Entire section of Adverse Event Reporting Requirements was replaced.

Amendment 3, August 28, 2003:

- Tumor assessments were changed from every 6 weeks to every three months after completion of protocol therapy on the CP arm.
- Liver Function Test Abnormalities information was added per mandate and Liver Function Test risks were added.
- Mandated bowel risk information was added.

Amendment 4, August 28, 2003:

- The statistical section was rewritten to remove the suspension as recommended by the ECOG DMB on April 22, 2003.
- The section on records to be kept was revised in its entirety.

Amendment 5, December 30, 2003:

- The protocol was revised to state that patients with> Grade 1 hemoptysis will have their protocol treatment discontinued.
- The bevacizumab side effects section was updated.
- The bevacizumab risk section was updated.

Amendment 6, January 29, 2004:

- The statistical section of the protocol was revised based on the recommendations made at the November 5, 2003 ECOG DMC meeting. The changes increased the number of patients and modified the monitoring plan to provide adequate power for smaller treatment differences than in the original design.
- The bevacizumab side effects section of the consent form was updated regarding the development of hemoptysis/pulmonary hemorrhage.

Amendment 7, August 13, 2004:

- Closed the correlative studies to patient recruitment.

Amendment 8, January 26, 2005:

- A section on arterial thromboembolic events was added to the bevacizumab dose modifications section.
- The bevacizumab side effects section was modified to include thrombosis and embolism and arterial thromboembolic events.
- The ICD was revised to include a "NOTE" on the risks of arterial thromboembolic adverse events.

Amendment 9, August 23, 2005:

- Changed the title of Appendix VIII from "NCI AdEERS Agent Specific Adverse Event List for Bevacizumab" to "Comprehensive Adverse Event and Potential Risks (CAEPR) List for Bevacizumab
- The bevacizumab drug information contained in section 8.3 of the protocol was revised in its entirety by a representative of ECOG's pharmacy committee to incorporate the new information contained in the CAEPR.
- The non-licensed production facility source of the bevacizumab and the possibility for potential differences in the licensed and unlicensed material was clarified in the protocol.

Changes in the Analyses performed (excerpted from the CSR)

The following analyses were specified in the Genentech-authored SAP but, as agreed to during the FDA (July 21, 2005 teleconference), were not performed by Genentech.

- Exploratory multivariate modeling of the effect of risk factors on PFS and objective response.
- Sensitivity analysis to assess impact of missing tumor assessments on PFS

The following analyses were performed by Genentech using a method different from that specified in Genentech's final SAP:

- PFS: Data for patients without disease progression or death at the time of analysis who had no tumor assessments were censored at the time of randomization rather than the time of randomization +1 day.
- PFS: Since patients in the CP arm could only receive treatment until Cycle 6, patients who discontinued study treatment prior to progression were not censored at the end of protocol therapy as stated in the SAP. All progression events that occurred were counted as events regardless of the patient's treatment status.
- Objective response: The 95% confidence interval for response rate was estimated using Fleiss' approximation instead of the approximate method given in the SAP.
- Duration of objective response: Since patients in the CP arm could only receive treatment until Cycle 6, the duration of objective response was calculated from date of complete or partial response until date of disease progression or death irrespective of number of days following discontinuation of study treatment.
- Time-to-onset adverse event analyses: Because the exact date of onset was not captured for all adverse events, hazard ratios were not calculated for selected adverse events.
- Differences for EPP patients: Non-protocol therapy administered prior to disease progression was not collected for EPP patients; as a result, censoring for non-protocol therapy as

specified in the SAP was not possible for the EPP patients. Blood pressure was not collected for EPP patients, so these patients were excluded from all blood pressure analyses. Bevacizumab dose information was not collected for EPP patients, so these patients are excluded from all analyses of bevacizumab dosing and dose modification.

- Because the dose of bevacizumab was not collected for EPP patients, in all safety analyses, patients were assigned to the treatment group to which they were randomized without referring to bevacizumab dosing information.
- The age categories for the exploratory analyses were changed from "< 40, 40–65, and > 65 years" to "< 40, 40–64, and ≥ 65 years." The following analyses were not planned in the SAP but were performed:
- The incidence of Grade 3–5 hemoptysis adverse events of patients enrolled before and after Amendment 1 (which excluded entry of patients who had a history of gross hemoptysis) was performed.
- Non-protocol therapy use both prior to and after progression, protocol deviation treatment summaries, and baseline disease and demographic characteristics were calculated separately for males and females.
- The use of TKI inhibitors after progression was not collected directly but was entered in the comments field of the follow-up therapy Form 1708 when non-protocol treatment was reported as "other." Genentech reviewed this field and presented the resulting tabulations for the overall population and by gender.

The following analyses were specified in the Genentech-authored SAP but, as agreed to by the FDA (21 July 2005 teleconference), were not to be performed because of the strong efficacy results. However, they were performed.

- Exploratory analyses of PFS and objective response by baseline characteristics subgroups
- Exploratory analyses of survival, PFS, and objective response with respect to baseline sum of the longest diameters in target lesions.

Appendix 2

Adverse Events Associated with Study Discontinuation

BV/CP Treatment Arm	
CARDIAC TROPONIN I	1
CARDIAC-ISCHEMIA	1
CNS HEMORRHAGE	1
CONDUCTION ABNORMALITY	1
DEPRESSION	1
DYSPEPSIA	1
DYSPHAGIA	1
FISTULA-ESOPHAGEAL	1
FISTULA-RECTAL/ANAL	1
HEMATURIA	1
HYPOALBUMINEMIA	1
INFECTION-OTHER	1
INJECTION SITE REACTION	1
MOUTH DRYNESS	1
MUSCULOSKELETAL-OTHER	1
NEUROPATHY-MOTOR	1
OSTEONECROSIS	1
PALPITATIONS	1
PNEUMOTHORAX	1
PRURITUS	1
PULMONARY FIBROSIS	1
PULMONARY-OTHER	1
SGOT	1
SGPT	1
STOMATITIS	1
SUPRAVENTRICULAR ARRHYTHMIAS	1
TRANSFUSION: PRBCS	1
TUMOR PAIN	1
URINARY FREQUENCY/URGENCY	1
VOICE CHANGES/STRIDOR	1
WEIGHT LOSS	1
WOUND - INFECTIOUS	1
ABDOMINAL PAIN	2
CEREBROVASCULAR ISCHEMIA	2
CONSTIPATION	2
EPISTAXIS	2
HYPERGLYCEMIA	2
HYPOCALCEMIA	2
HYPONATREMIA	2
HYPOXIA	2
INFECTION W/ UNKNOWN ANC	2
INFECTION W/O NEUTROPENIA	2
MELENA/GI BLEEDING	2
PLEURAL EFFUSION	2
SINUS TACHYCARDIA	2
VAGINAL BLEEDING	2
EDEMA	3
FEBRILE NEUTROPENIA	3
LYMPHOPENIA	3
BONE PAIN	4
COUGH	4
FEVER	4
HEMOPTYSIS	4
PLATELETS	4
PNEUMONITIS/PULMONARY INFILTRATES	4
RASH/DESQUAMATION	4
SYNCOPE	4
DIZZINESS/LIGHTHEADEDNESS	5
HEMOGLOBIN	5
MUSCLE WEAKNESS	5
VOMITING	5
HEADACHE	6

CP Treatment Arm	
ALKALOSIS	1
ANOREXIA	1
CARDIAC-ISCHEMIA	1
CARDIAC-LEFT VENTRICULAR FUNCTION	1
CEREBROVASCULAR ISCHEMIA	1
COGNITIVE DISTURBANCE	1
COUGH	1
DEPRESSION	1
DIZZINESS/LIGHTHEADEDNESS	1
DYSPHAGIA	1
DYSURIA	1
FEVER	1
GI-OTHER	1
HEMOGLOBIN	1
HEMOPTYSIS	1
HYPERTENSION	1
HYPONATREMIA	1
INFECTION W/ UNKNOWN ANC	1
MEMORY LOSS	1
METABOLIC-OTHER	1
NEUROLOGIC-OTHER	1
PELVIC PAIN	1
PROTEINURIA	1
SINUS TACHYCARDIA	1
SYNCOPE	1
TREMOR	1
TUMOR PAIN	1
ANXIETY/AGITATION	2
BONE PAIN	2
CONFUSION	2
DEHYDRATION	2
DIARRHEA	2
HYPOKALEMIA	2
INFECTION W/ GRADE 3 OR 4 NEUTROPENIA	2
INJECTION SITE REACTION	2
NEUROPATHY-MOTOR	2
PLATELETS	2
PNEUMONITIS/PULMONARY INFILTRATES	2
SGOT	2
SGPT	2
STOMATITIS	2
ARTHRALGIA	3
HYPOTENSION	3
HYPOXIA	3
LEUKOCYTES	3
VOMITING	3
MUSCLE WEAKNESS	5
NAUSEA	5
RASH/DESQUAMATION	5
THROMBOSIS/EMBOLISM	5
ALOPECIA	6
MYALGIA	6
ALLERGIC REACTION	9
DYSPNEA	9
NEUTROPHILS	13
FATIGUE	15
NEUROPATHY-SENSORY	21

HYPERTENSION	6		
NAUSEA	6		
ANOREXIA	7		
ARTHRALGIA	7		
DEHYDRATION	7		
HYPOTENSION	7		
LEUKOCYTES	7		
MYALGIA	7		
PROTEINURIA	7		
ALLERGIC REACTION	8		
ALOPECIA	8		
DIARRHEA	8		
NEUTROPHILS	12		
THROMBOSIS/EMBOLISM	12		
DYSPNEA	15		
NEUROPATHY-SENSORY	15		
FATIGUE	22		

Appendix 3

21-JUL-05 sBLA Teleconference meeting minutes

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 11, 2005

From: Sharon Sickafuse, CDER/ODE6/DRMP

To: IND 8648

Subject: July 21, 2005, teleconference with Genentech regarding the sBLA for NSCLC

Teleconference Date: July 21, 2005

Teleconference Requestor: Genentech, Inc.

Product: Bevacizumab

Proposed Use: Treatment of non-small cell lung cancer (NSCLC) in combination with platinum-containing chemotherapy

Teleconference Purpose: Discuss sBLA for this indication. Primary study data is from study E4599.

Background: Teleconference package is amendment 569 submitted on June 21, 2005. FDA responses to Genentech's questions were faxed to them on July 21, 2005. Below are

Genentech's questions, FDA responses and the discussion that occurred during the teleconference.

1. *Based on the significant survival results and the safety profile observed with bevacizumab in Study E4599 and additional efficacy and safety from Study AVF0757g, Genentech believe that the results from these two trials are sufficient to support a sBLA to extend the current indication for Avastin to the following: "Avastin, used in combination with platinum-based chemotherapy, is indicated for the first line treatment of patients with advanced or recurrent, non-squamous non-small cell lung cancer." Does the Agency agree that these two studies form the basis for this sBLA?*

   FDA agreed that studies E4599 and AVF0757g are sufficient to form the basis of an sBLA, however FDA cannot comment upon the indication statement prior to review of the submitted data.

2. *Does the Agency agree that the ECOG DMC interim analysis will form the primary basis for assessing statistical significance of the overall survival endpoint?*

   FDA agreed that the results of the two interim analyses for overall survival will form the basis for assessing statistical significance (i.e., for determining the final p-value). Any later analysis will be for descriptive purposes only.

   FDA asked Genentech to provide the results of the first interim analysis (including the timing of the analysis), the specific rule that was used for the timing of the analysis and the spending function that was used. Please also provide the timings (dates and number of events) of any informal interim analysis.

Discussion: Genentech agreed to provide the requested information. FDA asked if the patient population for the primary analysis will be the eligible population or the intent-to-treat population. Genentech stated that they will perform analyses with both populations, however the analysis on the intent-to-treat population (all randomized patients) will be the primary analysis.

3. *Does the Agency agree with Genentech's proposal for submission of the Clinical Study Report, patient narratives, Case Report Forms, and Case Report Tabulations?*

	Genentech Proposal	FDA
Patient Narratives	Experimental arm only Deaths-deaths < 30 d not due to PD and deaths > 30 d if thought due to bevacizumab AdEERs Report of Gr 3-4 AEs Gr 3-4 GI perforation or fistula Gr 1-4 Arterial TE Event Gr 3-4 Hemorrhage Secondary Malignancy Discontinuation due to AE	Narratives only for pts in the experimental arm Please also include narratives for CHF, gr 3-4 neuropathy, gr 3-4 HTN, and gr 3-4 proteinuria in the experimental arm.
CRFs	Pts requiring a narrative	CRFs for who die or

		discontinue therapy in both arms All CRFs should be available on request
SAS Datasets	All data collected on CRFs	Agree
SAS Programs	No Will provide variable derivations	Programs for primary and secondary analyses Programs for creating the derived datasets.

Discussion: Genentech agreed to provide all information requested by FDA as described in the table above.

- FDA asked that the programs used to create the derived datasets from the raw datasets be submitted. If these programs are not submitted and the FDA analyses based on the raw data lead to different results from those submitted results, the official results will be those from the FDA analyses.

Discussion: Genentech agreed to provide the programs used to create the derived datasets from the raw datasets.

- FDA advised that the inclusion of narratives from patients only in the experimental arm may negatively impact the adverse event profile of Bevacizumab by providing insufficient information for comparison to the control arm. In the absence of narratives from the control arm, all events will be attributed to Bevacizumab.

Discussion: Genentech expressed understanding, but still elected not to provide patient narratives for the control arm.

- FDA recommended that narratives should be based on information reported in both AdEERs and the clinical database. Please highlight discrepancies in the information provided in these two databases and included within a narrative.

Discussion: Genentech agreed to do so.

- FDA asked that narratives for adverse events leading to discontinuation list all adverse events that occurred within 30 days of discontinuation.

4. *Does the Agency agree with the proposed metadata for the datasets and statistical analyses to be submitted to the Agency?*

   FDA agreed and stated that there are a number of questions concerning the details of these datasets that can be discussed separately. Update: Teleconference held on

July 27 2005, between Genentech representatives and Drs. Maher, Summers, and Rothmann.

5. *Does the Agency agree with Genentech's proposal for the Summary of Clinical Efficacy?*

FDA agreed.

6. *Does the Agency agree with Genentech's proposal for the Summary of Clinical Safety?*

FDA agreed and understands that there will be no pooling of safety data of study E4599 and study AVF0757g.

7. *Assuming there are fewer than five patients receiving study drug at the time of filing, Genentech does not intend to submit a Safety Update to the sBLA. Does the Agency agree with this proposal?*

FDA asked Genentech to clarify whether this represents the number of patients receiving treatment at the time of database lock or at the time of filing.

Discussion: Genentech stated that as of July 21, 2005, approximately 10 patients are still receiving treatment. FDA recommended that Genentech provide a safety update including all serious adverse events which have occurred since the time of database lock. It is not necessary to recalculate each adverse event. Genentech agreed to provide a Safety Update.

8. *Based on the significant survival results and the safety profile observed with bevacizumab, Genentech believes that this sBLA is eligible for priority review. Does the Agency agree with this proposal?*

FDA agreed.

9. *Given the strength of the survival data and the known safety profile of bevacizumab, does the Agency agree that an Oncologic Drug Advisory Committee meeting is unnecessary?*

FDA stated that the need for an Advisory Committee meeting cannot be commented upon prior to review of the submission.

Additional FDA Comments:

10. Please provide additional information (such as mock up tables or listings) concerning the planned highlighting of adverse events that are only reported in AdEERs or only in the clinical database.

Discussion: FDA requested that the AdEERs information be in SAS format, not as a narrative across multiple columns as in the TRC supplement. FDA also asked that

Genentech explain the sources of supportive information in AdEERs. Genentech agreed to submit examples by the end of August of the way in which they intend to highlight differences in the AdEERs and clinical databases.

11. The pre-teleconference package contains a proposal to omit several of the analyses agreed to in the final statistical analysis plan. This is acceptable only if the datasets necessary to perform these analyses, along with appropriate flags, are included in this supplement. Early participation in this effort may facilitate the review process, especially if FDA analyses generate results on which Genentech would like to provide comment during the review.

Discussion: Genentech agreed to provide the datasets.

12. Under 21 CFR 314.50 (k) Genentech is required to act with due diligence to obtain the information necessary for financial disclosure certification. Given that all of the necessary documents were in fact collected, the proposal to include only documents collected after March 2002 does not meet the standard of due diligence.

Discussion: Genentech agreed to submit all financial disclosure information.

13. Please include all lot numbers and their site of manufacture in your submission.

Discussion: Genentech agreed to provide this information.

14. Prior to filing, please provide the following information, in tabular format, for each site.

Site #	# Screened	# Enrolled	# Deaths	# Discontinued	# SAEs	# Major Protocol Violations	Response Rate

Discussion: Genentech and ECOG said that the sites don't record the number of patients screened and FDA agreed that this information could be omitted from the above table. Genentech and ECOG also stated that events are not listed as serious in their database. FDA asked if they could provide the number of Grade 3-4 events rather than the number of serious events by site. They will be able to do so. FDA was concerned that the same patient may be counted multiple times (i.e, if the same patient had a Grade 4 event, discontinued, and later died) and may not provide a true picture of the toxicity at that site. FDA asked if Genentech could provide an additional column with a per patient incidence of these events at each site. Genentech agreed.

15. If IRB approvals and CVs are not included in the supplement, please provide a letter of cross reference to the NCI master file or IND where this information resides. In this letter, you will need to specify the date of submission, the volume number, and the page number.

FDA Attendees:

Center for Drug Evaluation and Research

Office of Oncology Drug Products
Division of Biologic Oncology Products
Patricia Keegan, M.D.
Ellen Maher, M.D.
Sharon Sickafuse, M.S.
Jeff Summers, M.D.

Office of Biostatistics
Biologic Therapeutic Statistical Staff
Mark Rothmann, Ph.D.

Sponsor Attendees:

Genentech, Inc.

Lisa Bell, Ph.D., Senior Manager, Regulatory Affairs
Isaiah Dimery, M.D., Director, BioOncology
Benjamin Lyons, Ph.D., Senior Biostatistician, Biostatistics
Sandra Minjoe, M.S., Principal Statistical Programmer Analyst, Statistical Programming
Michael Ostland, Ph.D., Associate Director, Biostatistics
David Ramies, M.D., Medical Director
Todd Rich, M.D., VP of Medical Affairs
Michelle Rohrer, Ph.D., Director, Regulatory Affairs
Jamey Skillings, M.D., Group Director, BioOncology
Kathleen Winson, M.A., Operations Team Leader, BioOncology

ECOG

Robert Gray, Ph.D., Group Statistician
Alan Sandler, M.D., Study Chair
Joan Schiller, M.D., Thoracic Committee Chair

NCI

Helen Chen, Senior Investigator, CTEP
Scott Saxman, M.D., Senior Investigator, Clinical Investigations Branch, CTEP, DCTD

10.1 Review of Individual Study Reports

The salient points of the two study reports submitted in this efficacy supplement application, AVF0757g and E4599, are reviewed in sections 1-9.

10.2 Line-by-Line Labeling Review

Final Labeling Text

AVASTIN®
(Bevacizumab)

For Intravenous Use

WARNINGS

Gastrointestinal Perforations

AVASTIN administration can result in the development of gastrointestinal perforation, in some instances resulting in fatality. Gastrointestinal perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with AVASTIN (i.e., was not correlated to duration of exposure). The incidence of gastrointestinal perforation (gastrointestinal perforation, fistula formation, and/or intra-abdominal abscess) in patients with colorectal cancer and in patients with non-small cell lung cancer (NSCLC) receiving AVASTIN was 2.4 % and 0.9%, respectively. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and vomiting. Gastrointestinal perforation should be included in the differential diagnosis of patients presenting with abdominal pain on AVASTIN. AVASTIN therapy should be permanently discontinued in patients with gastrointestinal perforation. (See **WARNINGS: Gastrointestinal Perforations** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

Wound Healing Complications

AVASTIN administration can result in the development of wound dehiscence, in some instances resulting in fatality. AVASTIN therapy should be permanently discontinued in patients with wound dehiscence requiring medical intervention. The appropriate interval between termination of AVASTIN and subsequent elective surgery required to avoid the risks of impaired wound healing/wound dehiscence has not been determined. (See **WARNINGS: Wound Healing Complications** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

Hemorrhage

Fatal pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and AVASTIN. The incidence of severe or fatal hemoptysis was 31% in patients with squamous histology and 2.3% in patients with NSCLC excluding predominant squamous histology. Patients with recent hemoptysis (≥ ½ tsp of red blood) should not receive AVASTIN. (See **WARNINGS: Hemorrhage, ADVERSE REACTIONS: Hemorrhage,** and **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

DESCRIPTION

AVASTIN® (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and has a molecular weight of approximately 149 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion. AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of Bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

Pharmacokinetics

The pharmacokinetic profile of Bevacizumab was assessed using an assay that measures total serum Bevacizumab concentrations (i.e., the assay did not distinguish between free Bevacizumab

and Bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of AVASTIN weekly, every 2 weeks, or every 3 weeks, the estimated half-life of Bevacizumab was approximately 20 days (range 11–50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of Bevacizumab every 2 weeks was 2.8.

The clearance of Bevacizumab varied by body weight, by gender, and by tumor burden. After correcting for body weight, males had a higher Bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger V_c (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher Bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. In a randomized study of 813 patients (Study 1), there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with AVASTIN as compared to females and patients with low tumor burden. The relationship between Bevacizumab exposure and clinical outcomes has not been explored.

Special Populations

Analyses of demographic data suggest that no dose adjustments are necessary for age or sex.

Patients with renal impairment. No studies have been conducted to examine the pharmacokinetics of Bevacizumab in patients with renal impairment.

Patients with hepatic dysfunction. No studies have been conducted to examine the pharmacokinetics of Bevacizumab in patients with hepatic impairment.

CLINICAL STUDIES

AVASTIN® In Metastatic Colorectal Cancer (mCRC)

The safety and efficacy of AVASTIN in the treatment of patients with metastatic carcinoma of the colon or rectum were studied in three randomized, controlled clinical trials in combination with intravenous 5-fluorouracil–based chemotherapy. The activity of AVASTIN in patients with metastatic colorectal cancer that progressed on or after receiving both irinotecan based- and oxaliplatin based- chemotherapy regimens was evaluated in an open-access trial in combination with intravenous 5-fluorouracil-based chemotherapy.

AVASTIN in Combination with Bolus-IFL

Study 1 was a randomized, double-blind, active-controlled clinical trial evaluating AVASTIN as first-line treatment of metastatic carcinoma of the colon or rectum. Patients were randomized to bolus-IFL (irinotecan 125 mg/m^2 IV, 5-fluorouracil 500 mg/m^2 IV, and leucovorin 20 mg/m^2 IV given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus AVASTIN (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV plus AVASTIN (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, when the toxicity of AVASTIN in combination with the bolus-IFL regimen was deemed acceptable.

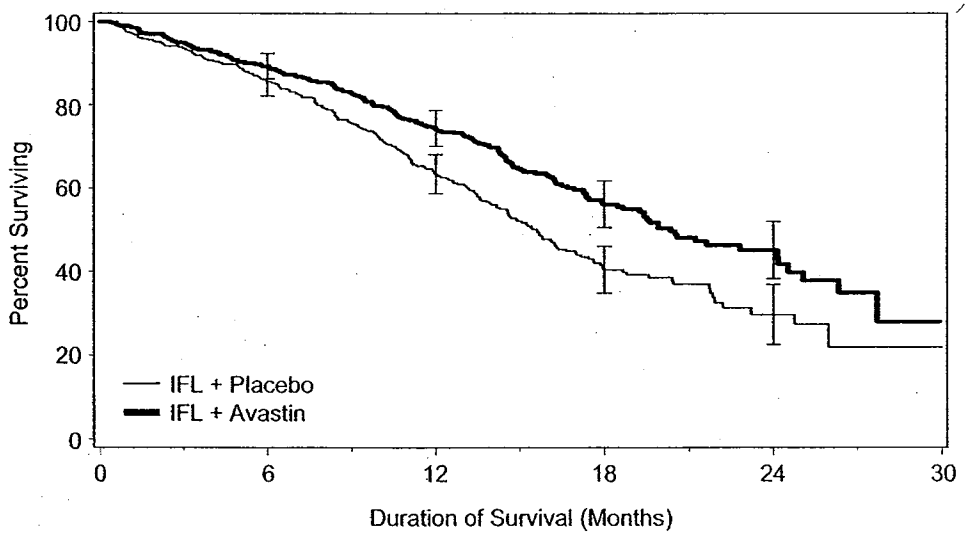
Of the 813 patients randomized to Arms 1 and 2, the median age was 60, 40% were female, and 79% were Caucasian. Fifty-seven percent had an ECOG performance status of 0. Twenty-one percent had a rectal primary and 28% received prior adjuvant chemotherapy. In the majority of patients, 56%, the dominant site of disease was extra-abdominal, while the liver was the dominant site in 38% of patients. Results are presented in Table 1 and Figure 1.

Table 1
Study 1 Efficacy Results

	IFL + Placebo	IFL + AVASTIN 5 mg/kg q 2 wks
Number of Patients	411	402
Overall Survival[a]		
Median (months)	15.6	20.3
Hazard ratio		0.66
Progression-free Survival[a]		
Median (months)	6.2	10.6
Hazard ratio		0.54
Overall Response Rate[b]		
Rate (percent)	35%	45%
Duration of Response		
Median (months)	7.1	10.4

[a] $p<0.001$ by stratified logrank test.
[b] $p<0.01$ by χ^2 test.

Figure 1
Duration of Survival in Study 1



Error bars represent 95% confidence intervals.

The clinical benefit of AVASTIN, as measured by survival in the two principal arms, was seen in the subgroups defined by age (<65 yrs, ≥65 yrs) and gender.

Among the 110 patients enrolled in Arm 3, median overall survival was 18.3 months, median progression-free survival was 8.8 months, overall response rate was 39%, and median duration of response was 8.5 months.

AVASTIN in Combination with 5-FU/LV Chemotherapy

Study 2 was a randomized, active-controlled clinical trial testing AVASTIN in combination with 5-FU/LV as first-line treatment of metastatic colorectal cancer. Patients were randomized to receive 5-FU/LV (5-fluorouracil 500 mg/m^2, leucovorin 500 mg/m^2 weekly for 6 weeks every 8 weeks) or 5-FU/LV plus AVASTIN (5 mg/kg every 2 weeks) or 5-FU/LV plus AVASTIN (10 mg/kg every 2 weeks). The primary endpoints of the trial were objective response rate and progression-free survival. Results are presented in Table 2.

Table 2
Study 2 Efficacy Results

	5-FU/LV	5-FU/LV + AVASTIN 5 mg/kg	5-FU/LV + AVASTIN 10 mg/kg
Number of Patients	36	35	33
Overall Survival			
Median (months)	13.6	17.7	15.2
Progression-free Survival			
Median (months)	5.2	9.0	7.2
Overall Response Rate			
Rate (percent)	17	40	24

Progression-free survival was significantly longer in patients receiving 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not receiving AVASTIN. However, overall survival and overall response rate were not significantly different. Outcomes for patients receiving 5-FU/LV plus AVASTIN at 10 mg/kg were not significantly different than for patients who did not receive AVASTIN.

AVASTIN in Combination with 5-FU/LV and Oxaliplatin Chemotherapy

Study 3 was an open-label, randomized, 3-arm, active-controlled, multicenter clinical trial evaluating AVASTIN alone, AVASTIN in combination with 5-FU/LV and oxaliplatin (FOLFOX4), and FOLFOX4 alone in the second-line treatment of metastatic carcinoma of the colon or rectum. Patients were previously treated with irinotecan and 5-FU for initial therapy for

metastatic disease or as adjuvant therapy. Patients were randomized to FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2 concurrently IV, then 5-FU 400 mg/m^2 IV bolus followed by 600 mg/m^2 continuously IV; Day 2: leucovorin 200 mg/m^2 IV, then 5-FU 400 mg/m^2 IV bolus followed by 600 mg/m^2 continuously IV; repeated every 2 weeks), FOLFOX4 plus AVASTIN, or AVASTIN monotherapy. AVASTIN was administered at a dose of 10 mg/kg every 2 weeks and for patients in the FOLFOX4 plus AVASTIN arm, prior to the FOLFOX4 chemotherapy on Day 1.

Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female, 87% were Caucasian, and 49% had an ECOG performance status of 0. Twenty-six percent had received prior radiation therapy, and 80% received prior adjuvant chemotherapy. Ninety-nine percent received prior irinotecan, with or without 5-FU for metastatic colorectal cancer, and 1% received prior irinotecan and 5-FU as adjuvant therapy.

The AVASTIN monotherapy arm of Study 3 was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee (DMC), based on evidence of decreased survival in the AVASTIN alone arm as compared to the FOLFOX4 alone arm. In the two remaining study arms, overall survival (OS) was significantly longer in patients receiving AVASTIN in combination with FOLFOX4 as compared to those receiving FOLFOX4 alone (median OS 13.0 mos vs. 10.8 mos; hazard ratio 0.75 [95% CI 0.63, 0.89], p=0.001 stratified log rank test). In addition, patients treated with AVASTIN in combination with FOLFOX4 were reported to have significantly longer progression-free survival and a higher overall response rate based on investigator assessment. The clinical benefit of AVASTIN, as measured by survival, was seen in the subgroups defined by age (<65 yrs, ≥65 yrs) and gender.

AVASTIN in Third-Line Metastatic Colorectal Cancer

Study 4 was an open access, multicenter, single arm study that evaluated the activity of AVASTIN in combination with bolus or infusional 5-FU/LV in 339 patients with metastatic colorectal cancer with disease progression following both irinotecan- and oxaliplatin-containing chemotherapy regimens. The majority (73%) of patients received concurrent 5-FU/LV according to a bolus regimen.

There was one objective partial response in the first 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

AVASTIN® In Unresectable Non-Squamous, Non-Small Cell Lung Cancer (NSCLC)

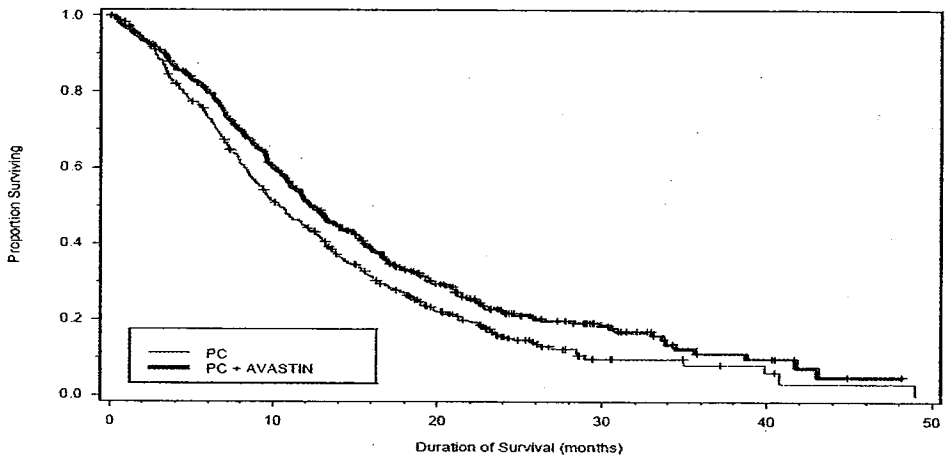
The safety and efficacy of AVASTIN as first-line treatment of patients with locally advanced, metastatic, or recurrent non-squamous, NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study (Study 5, n=878), supported by a randomized, dose ranging, active controlled Phase 2 study (Study 6, n=98).

In Study 5, chemotherapy-naïve patients with locally advanced, metastatic or recurrent non-squamous NSCLC were randomized (1:1) to receive six cycles of paclitaxel 200 mg/m^2 and carboplatin AUC=6.0, both by IV infusion on day 1 (PC) or PC in combination with AVASTIN at a dose of 15 mg/kg by IV infusion on day 1 (PC plus AVASTIN). After completion or upon discontinuation of chemotherapy, patients in the PC plus AVASTIN arm continued to receive AVASTIN alone until disease progression or until unacceptable toxicity. Cycles were repeated every 21 days. Patients with predominant squamous histology (mixed cell type tumors only), central nervous system (CNS) metastasis, gross hemoptysis ($\geq$ 1/2 tsp of red blood), or unstable angina and those receiving therapeutic anticoagulation were excluded. The main outcome measure of the study was duration of survival.

Among the 878 patients randomized to the two treatment arms, the median age was 63, 46% were female, 43% were $\geq$ age 65, and 28% had $\geq$ 5% weight loss at study entry. Eleven percent had recurrent disease and of the remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease. The survival curves are presented in Figure 2. Overall survival was statistically significantly higher among patients receiving PC plus AVASTIN compared with those receiving PC alone; median OS was 12.3 mos vs. 10.3 mos (hazard ratio 0.80 [repeated 95% CI 0.68, 0.94], final p- value 0.013, stratified log-rank test). Based on investigator assessment which was not independently verified, patients were reported to have longer progression-free survival with AVASTIN in combination with PC compared to PC alone.

Figure 2

Duration of Survival in Study 5



In an exploratory analyses across patient subgroups, the impact of AVASTIN on overall survival was less robust in the following: women [HR = 0.99 (95% CI: 0.79, 1.25)], age ≥ 65 years [HR = 0.91 (95% CI: 0.72, 1.14)] and patients with ≥ 5% weight loss at study entry [HR = 0.96 (95% CI: 0.73, 1.26)].

INDICATIONS AND USAGE

AVASTIN®, in combination with intravenous 5-fluorouracil–based chemotherapy, is indicated for first-or second-line treatment of patients with metastatic carcinoma of the colon or rectum.

AVASTIN®, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous, non-small cell lung cancer.

CONTRAINDICATIONS

None.

WARNINGS

Gastrointestinal Perforations (See DOSAGE AND ADMINISTRATION: Dose Modifications)

Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation and in some instances with fatal outcome, occurs at an increased incidence in patients receiving AVASTIN as compared to controls. In Studies 1, 2, and 3, the incidence of gastrointestinal

perforation (gastrointestinal perforation, fistula formation, and/or intra-abdominal abscess) in patients receiving AVASTIN was 2.4%. These episodes occurred with or without intra-abdominal abscesses and at various time points during treatment. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and emesis.

In post-marketing clinical studies and reports, gastrointestinal perforation, fistula and/or intra-abdominal abscess occurred in patients receiving AVASTIN for colorectal and for other types of cancer. The overall incidence in clinical studies was 1%, but may be higher in some cancer settings. Of the reported events, approximately 30% were fatal. Patients with gastrointestinal perforation, regardless of underlying cancer, typically present with abdominal pain, nausea and fever. Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of AVASTIN, with most events occurring within the first 50 days.

Permanently discontinue AVASTIN in patients with gastrointestinal perforation.

Wound Healing Complications (See DOSAGE AND ADMINISTRATION: Dose Modifications)

AVASTIN impairs wound healing in animal models. In clinical studies of AVASTIN, patients were not allowed to receive AVASTIN until at least 28 days had elapsed following surgery. In clinical studies of AVASTIN in combination with chemotherapy, there were 6 instances of dehiscence among 788 patients (0.8%).

The appropriate interval between discontinuation of AVASTIN and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined. In Study 1, 39 patients who received bolus-IFL plus AVASTIN underwent surgery following AVASTIN therapy; of these patients, six (15%) had wound healing/bleeding complications. In the same study, 25 patients in the bolus-IFL arm underwent surgery; of these patients, one of 25 (4%) had wound healing/bleeding complications. The longest interval between last dose of study drug and dehiscence was 56 days; this occurred in a patient on the bolus-IFL plus AVASTIN arm.

The interval between termination of AVASTIN and subsequent elective surgery should take into consideration the calculated half-life of AVASTIN (approximately 20 days).

Discontinue AVASTIN in patients with wound healing complications requiring medical intervention.

Hemorrhage (See DOSAGE AND ADMINISTRATION: Dose Modifications)
Two distinct patterns of bleeding have occurred in patients receiving AVASTIN. The first is minor hemorrhage, most commonly NCI-CTC Grade 1 epistaxis. The second is serious, and in some cases fatal, hemorrhagic events.

In Study 6, four of 13 (31%) AVASTIN-treated patients with squamous cell histology and two of 53 (4%) AVASTIN-treated patients with histology other than squamous cell, experienced serious or fatal pulmonary hemorrhage as compared to none of the 32 (0%) patients receiving chemotherapy alone. Of the patients experiencing pulmonary hemorrhage requiring medical intervention, many had cavitation and/or necrosis of the tumor, either pre-existing or developing during AVASTIN therapy. In Study 5, the rate of pulmonary hemorrhage requiring medical intervention for the PC plus AVASTIN arm was 2.3% (10 of 427) compared to 0.5% (2 of 441) for the PC alone arm. There were seven deaths due to pulmonary hemorrhage reported by investigators in the PC plus AVASTIN arm as compared to one in the PC alone arm. Generally, these serious hemorrhagic events presented as major or massive hemoptysis without an antecedent history of minor hemoptysis during Avastin therapy. Do not administer AVASTIN to patients with recent history of hemoptysis of ≥ ½ tsp of red blood. Other serious bleeding events occurring in patients receiving AVASTIN across all indications include gastrointestinal hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke. Some of these events were fatal. (See **ADVERSE REACTIONS: Hemorrhage.)**

The risk of central nervous system (CNS) bleeding in patients with CNS metastases receiving AVASTIN has not been evaluated because these patients were excluded from late stage clinical studies following development of CNS hemorrhage in a patient with a CNS metastasis in a Phase 1 study.

Discontinue AVASTIN in patients with serious hemorrhage (i.e., requiring medical intervention) and initiate aggressive medical management. (See **ADVERSE REACTIONS: Hemorrhage.)**

Arterial Thromboembolic Events (see DOSAGE AND ADMINISTRATION: Dose Modifications and PRECAUTIONS: Geriatric Use)

Arterial thromboembolic events (ATE) occurred at a higher incidence in patients receiving AVASTIN in combination with chemotherapy as compared to those receiving chemotherapy alone. ATE included cerebral infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), angina, and a variety of other ATE. These events were fatal in some instances.

In a pooled analysis of randomized, controlled clinical trials involving 1745 patients, the incidence of ATE was 4.4% among patients treated with AVASTIN in combination with chemotherapy and 1.9% among patients receiving chemotherapy alone. Fatal outcomes for these events occurred in 7 of 963 patients (0.7%) who were treated with AVASTIN in combination with chemotherapy, compared to 3 of 782 patients (0.4%) who were treated with chemotherapy alone. The incidences of both cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial events (2.1% vs. 1.0%) were increased in patients receiving AVASTIN compared to chemotherapy alone. The relative risk of ATE was greater in patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%). (See **PRECAUTIONS: Geriatric Use.)**

The safety of resumption of AVASTIN therapy after resolution of an ATE has not been studied. Permanently discontinue AVASTIN in patients who experience a severe ATE during treatment. (See **DOSAGE AND ADMINISTRATION: Dose Modifications** and **PRECAUTIONS: Geriatric Use.)**

Hypertension (See DOSAGE AND ADMINISTRATION: Dose Modifications)

The incidence of severe hypertension was increased in patients receiving AVASTIN as compared to controls. Across clinical studies the incidence of NCI-CTC Grade 3 or 4 hypertension ranged from 8-18%.

Medication classes used for management of patients with NCI-CTC Grade 3 hypertension receiving AVASTIN included angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers. Development or worsening of hypertension can require hospitalization or require discontinuation of AVASTIN in up to 1.7% of patients. Hypertension can persist after discontinuation of AVASTIN. Complications can include hypertensive encephalopathy (in some cases fatal) and CNS hemorrhage.

In the post-marketing experience, acute increases in blood pressure associated with initial or subsequent infusions of AVASTIN have been reported (see **PRECAUTIONS: Infusion Reactions**). Some cases were serious and associated with clinical sequelae.

Permanently discontinue AVASTIN in patients with hypertensive crisis or hypertensive encephalopathy. Temporarily suspend AVASTIN in patients with severe hypertension that is not controlled with medical management. (See **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (See DOSAGE AND ADMINISTRATION: Dose Modifications)

RPLS has been reported in clinical studies (with an incidence of <0.1%) and in post-marketing experience. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present, but is not necessary for diagnosis of RPLS. Magnetic Resonance Imaging (MRI) is necessary to confirm the diagnosis of RPLS. The onset of symptoms has been reported to occur from 16 hours to 1 year after initiation of AVASTIN.

In patients developing RPLS, discontinue AVASTIN and initiate treatment of hypertension, if present. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating AVASTIN therapy in patients previously experiencing RPLS is not known.

Neutropenia and Infection (See PRECAUTIONS: Geriatric Use and ADVERSE REACTIONS: Neutropenia and Infection)

Increased rates of severe neutropenia, febrile neutropenia, and infection with severe neutropenia (including some fatalities) have been observed in patients treated with myelosuppressive chemotherapy plus AVASTIN. (See **PRECAUTIONS: Geriatric Use** and **ADVERSE REACTIONS: Neutropenia and Infection.)**

Proteinuria (See DOSAGE AND ADMINISTRATION: Dose Modifications)

The incidence and severity of proteinuria is increased in patients receiving AVASTIN as compared to control. In Studies 1, 3 and 5 the incidence of NCI-CTC Grade 3 and 4 proteinuria, characterized as >3.5 gm/24 hours, ranged up to 3.0% in AVASTIN-treated patients.

Nephrotic syndrome occurred in seven of 1459 (0.5%) patients receiving AVASTIN in clinical studies. One patient died and one required dialysis. In three patients, proteinuria decreased in severity several months after discontinuation of AVASTIN. No patient had normalization of urinary protein levels (by 24-hour urine) following discontinuation of AVASTIN.

The highest incidence of proteinuria was observed in a dose-ranging, placebo-controlled, randomized study of AVASTIN in patients with metastatic renal cell carcinoma, an indication for which AVASTIN is not approved, 24-hour urine collections were obtained in approximately half the patients enrolled. Among patients in whom 24-hour urine collections were obtained, four of 19 (21%) patients receiving AVASTIN at 10 mg/kg every two weeks, two of 14 (14%) patients receiving AVASTIN at 3 mg/kg every two weeks, and none of the 15 placebo patients experienced NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

Discontinue AVASTIN in patients with nephrotic syndrome. The safety of continued AVASTIN treatment in patients with moderate to severe proteinuria has not been evaluated. In most clinical studies, AVASTIN was interrupted for ≥2 grams of proteinuria/24 hours and resumed when proteinuria was <2 gm/24 hours. Patients with moderate to severe proteinuria based on 24-hour collections should be monitored regularly until improvement and/or resolution is observed. (See **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Congestive Heart Failure

Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left ventricular dysfunction, was reported in 25 of 1459 (1.7%) patients receiving AVASTIN in clinical studies. The risk of CHF appears to be higher in patients receiving AVASTIN who have received prior or concurrent anthracyclines. In a controlled study in patients with breast cancer (an unlabelled indication), the incidence of CHF was higher in the AVASTIN plus chemotherapy arm as compared to the chemotherapy alone arm. Congestive heart failure occurred in 13 of 299 (4%) patients who received prior anthracyclines and/or left chest wall irradiation. Congestive heart failure occurred in six of 44 (14%) patients with relapsed acute leukemia (an unlabelled indication) receiving AVASTIN and concurrent anthracyclines in a single arm study.

The safety of continuation or resumption of AVASTIN in patients with cardiac dysfunction has not been studied.

PRECAUTIONS

General

Use AVASTIN with caution in patients with known hypersensitivity to AVASTIN or any component of this drug product.

Infusion Reactions

In clinical studies, infusion reactions with the first dose of AVASTIN were uncommon (<3%) and severe reactions occurred in 0.2% of patients. Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, NCI-CTC Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Adequate information on rechallenge is not available. AVASTIN infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with AVASTIN after experiencing a severe infusion reaction.

Surgery

AVASTIN therapy should not be initiated for at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of AVASTIN. Because of the potential for impaired wound healing, AVASTIN should be suspended prior to elective surgery.
The appropriate interval between the last dose of AVASTIN and elective surgery is unknown; however, the half-life of AVASTIN is estimated to be 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and the interval chosen should take into consideration the half-life of the drug. (See **WARNINGS: Gastrointestinal Perforations** and **Wound Healing Complications.)**

Cardiovascular Disease

Patients were excluded from participation in AVASTIN clinical trials if, in the previous year, they had experienced clinically significant cardiovascular disease. In an exploratory analysis pooling the data from five randomized, placebo-controlled, clinical trials conducted in patients without a recent history of clinically significant cardiovascular disease, the overall incidence of arterial thromboembolic events, the incidence of fatal arterial thromboembolic events, and the incidence of cardiovascular thromboembolic events were increased in patients receiving AVASTIN plus chemotherapy as compared to chemotherapy alone.

Laboratory Tests

Blood pressure monitoring should be conducted every two to three weeks during treatment with AVASTIN. Patients who develop hypertension on AVASTIN may require blood pressure monitoring at more frequent intervals. Patients with AVASTIN-induced or -exacerbated hypertension who discontinue AVASTIN should continue to have their blood pressure monitored at regular intervals.

Patients receiving AVASTIN should be monitored for the development or worsening of proteinuria with serial urinalyses. Patients with a 2+ or greater urine dipstick reading should undergo further assessment, e.g., a 24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Drug Interactions

No formal drug interaction studies with anti-neoplastic agents have been conducted. In Study 1, patients with colorectal cancer were given irinotecan/5-FU/leucovorin (bolus-IFL) with or without AVASTIN. Irinotecan concentrations were similar in patients receiving bolus-IFL alone and in combination with AVASTIN. The concentrations of SN38, the active metabolite of irinotecan, were on average 33% higher in patients receiving bolus-IFL in combination with AVASTIN when compared with bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus AVASTIN had a higher incidence of NCI-CTC Grade 3–4 diarrhea and neutropenia. Due to high inter-patient variability and limited sampling, the extent of the increase in SN38 levels in patients receiving concurrent irinotecan and AVASTIN is uncertain.

In Study 6, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with AVASTIN. However, 3 of the 8 patients receiving AVASTIN plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without AVASTIN had a greater paclitaxel exposure at Day 63 than at Day 0.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity data are available for AVASTIN in animals or humans.

AVASTIN may impair fertility. Dose-related decreases in ovarian and uterine weights, endometrial proliferation, number of menstrual cycles, and arrested follicular development or

absent corpora lutea were observed in female cynomolgus monkeys treated with 10 or 50 mg/kg of AVASTIN for 13 or 26 weeks. Following a 4- or 12-week recovery period, which examined only the high–dose group, trends suggestive of reversibility were noted in the two females for each regimen that were assigned to recover. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point, but uterine weight decreases were still notable, corpora lutea were absent in 1 out of 2 animals, and the number of menstrual cycles remained reduced (67%).

Pregnancy Category C

AVASTIN has been shown to be teratogenic in rabbits when administered in doses that approximate the human dose on a mg/kg basis. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions, and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested.

Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of AVASTIN is likely to result in adverse effects on pregnancy. There are no adequate and well-controlled studies in pregnant women. AVASTIN should be used during pregnancy or in any woman not employing adequate contraception only if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of AVASTIN to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving AVASTIN, she should be apprised of the potential hazard to the fetus and/or the potential risk of loss of pregnancy. Patients who discontinue AVASTIN should also be counseled concerning the prolonged exposure following discontinuation of therapy (half-life of approximately 20 days) and the possible effects of AVASTIN on fetal development.

Nursing Mothers

It is not known whether AVASTIN is secreted in human milk. Because human IgG1 is secreted into human milk, the potential for absorption and harm to the infant after ingestion is unknown. Women should be advised to discontinue nursing during treatment with AVASTIN and for a prolonged period following the use of AVASTIN, taking into account the half-life of the product, approximately 20 days [range 11–50 days]. (See **CLINICAL PHARMACOLOGY: Pharmacokinetics.)**

Pediatric Use

The safety and effectiveness of AVASTIN in pediatric patients has not been studied. However, physeal dysplasia was observed in juvenile cynomolgus monkeys with open growth plates treated for four weeks with doses that were less than the recommended human dose based on mg/kg and exposure. The incidence and severity of physeal dysplasia were dose-related and were at least partially reversible upon cessation of treatment.

Geriatric Use

In Study 1, NCI-CTC Grade 3–4 adverse events were collected in all patients receiving study drug (396 bolus-IFL plus placebo; 392 bolus-IFL plus AVASTIN; 109 5-FU/LV plus AVASTIN), while NCI-CTC Grade 1 and 2 adverse events were collected in a subset of 309 patients. There were insufficient numbers of patients 65 years and older in the subset in which NCI-CTC Grade 1-4 adverse events were collected to determine whether the overall adverse event profile was different in the elderly as compared to younger patients. Among the 392 patients receiving bolus-IFL plus AVASTIN, 126 were at least 65 years of age. Severe adverse events that occurred at a higher incidence ($\geq$2%) in the elderly when compared to those less than 65 years were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of AVASTIN on overall survival was similar in elderly patients as compared to younger patients.

In Study 3, patients age 65 and older receiving AVASTIN plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 5 patients age 65 and older receiving carboplatin, paclitaxel, and AVASTIN had a greater relative risk for proteinuria as compared to younger patients.

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients age 65 or older and 1127 patients less than 65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving AVASTIN with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).
(See **WARNINGS: Arterial Thromboembolic Events.**)

ADVERSE REACTIONS

The most serious adverse reactions in patients receiving AVASTIN were:

- Gastrointestinal Perforations (see **WARNINGS**)
- Wound Healing Complications (see **WARNINGS**)
- Hemorrhage (see **WARNINGS**)
- Arterial Thromboembolic Events (see **WARNINGS**)
- Hypertensive Crises (see **WARNINGS: Hypertension**)
- Reversible Posterior Leukoencephalopathy Syndrome (see **WARNINGS**)
- Neutropenia and Infection (see **WARNINGS**)
- Nephrotic Syndrome (see **WARNINGS: Proteinuria**)
- Congestive Heart Failure (see **WARNINGS**)

The most common adverse events in patients receiving AVASTIN were asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to AVASTIN in 1529 patients, including 665 receiving AVASTIN for at least 6 months and 199 receiving AVASTIN for at least one year.

AVASTIN was studied primarily in placebo- and active-controlled trials (n = 501, and n = 1028, respectively).

Gastrointestinal Perforation

The incidence of gastrointestinal perforation across all studies ranged from 0-3.7%. The incidence of gastrointestinal perforation, in some cases fatal, in patients with mCRC receiving AVASTIN alone or in combination with chemotherapy was 2.4% compared to 0.3% in patients receiving only chemotherapy. The incidence of gastrointestinal perforation in NSCLC patients receiving AVASTIN was 0.9% compared to 0% in patients receiving only chemotherapy. (See **WARNINGS: Gastrointestinal Perforations** and **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving AVASTIN as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus AVASTIN as compared to 4% (1/25) of patients who received bolus-IFL alone. In the same study, the incidence of wound dehiscence was also higher in the AVASTIN-treated patients (1% vs. 0.5%).

Hemorrhage

Severe or fatal hemorrhages, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five fold more frequently in AVASTIN treated patients compared to patients treated with chemotherapy alone. NCI-CTC Grade 3-5 hemorrhagic events occurred in 4.7% of NSCLC patients and 5.2% of mCRC patients receiving AVASTIN compared to 1.1% and 0.7% for the control groups respectively. (See **WARNINGS: Hemorrhage.)**

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus AVASTIN compared with patients receiving bolus-IFL plus placebo. These events were generally mild in severity (NCI-CTC Grade 1) and resolved without medical intervention. Additional mild to moderate hemorrhagic events reported more frequently in patients receiving bolus-IFL plus AVASTIN when compared to those receiving bolus-IFL plus placebo included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal

hemorrhage (4% vs. 2%). (See **WARNINGS: Hemorrhage** and **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Arterial Thromboembolic Events

The incidence of arterial thromboembolic events was increased in NSCLC patients receiving PC plus AVASTIN (3.0%) compared with patients receiving PC alone (1.4%). Five events were fatal in the PC plus AVASTIN arm, compared with 1 event in the PC alone arm. This increased risk is consistent with that observed in patients with mCRC. (See **WARNINGS: Arterial Thromboembolic Events, DOSAGE AND ADMINISTRATION: Dose Modifications,** and **PRECAUTIONS: Geriatric Use.)**

Venous Thromboembolic Events

The incidence of NCI-CTC Grade 3–4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving AVASTIN with chemotherapy as compared to those receiving chemotherapy alone. In addition, in patients with mCRC the risk of developing a second subsequent thromboembolic event in patients receiving AVASTIN and chemotherapy is increased compared to patients receiving chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus AVASTIN arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus AVASTIN and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of NCI-CTC Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus AVASTIN and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following NCI-CTC Grade 3 and 4 venous thromboembolic events was higher in patients receiving bolus-IFL plus AVASTIN as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

Hypertension

Fatal CNS hemorrhage complicating AVASTIN induced hypertension can occur.

In Study 1, the incidences of hypertension and of severe hypertension were increased in patients with mCRC receiving AVASTIN compared to those receiving chemotherapy alone (see Table 3).

Table 3
Incidence of Hypertension and Severe Hypertension in Study 1

	Arm 1 IFL+Placebo (n=394)	Arm 2 IFL+AVASTIN (n=392)	Arm 3 5-FU/LV+AVASTIN (n=109)
Hypertension[a] (>150/100 mmHg)	43%	60%	67%
Severe Hypertension[a] (>200/110 mmHg)	2%	7%	10%

[a] This includes patients with either a systolic or diastolic reading greater than the cutoff value on one or more occasions.

Among patients with severe hypertension in the AVASTIN arms, slightly over half the patients (51%) had a diastolic reading greater than 110 mmHg associated with a systolic reading less than 200 mmHg.

Similar results were seen in patients receiving AVASTIN alone or in combination with FOLFOX4 or carboplatin and paclitaxel. (See **WARNINGS: Hypertension** and **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

Neutropenia and Infection

An increased incidence of neutropenia has been reported in patients receiving AVASTIN and chemotherapy compared to chemotherapy alone. In Study 1, the incidence of NCI-CTC Grade 3 or 4 neutropenia was increased in patients with mCRC receiving IFL+AVASTIN (21%) compared to patients receiving IFL alone (14%). In Study 5, the incidence of NCI-CTC Grade 4 neutropenia was increased in patients with NSCLC receiving PC plus AVASTIN (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus AVASTIN vs. 1.8% for PC alone). There were 19 (4.5%) infections with NCI-CTC Grade 3 or 4 neutropenia in the PC plus AVASTIN arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus AVASTIN arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

Proteinuria

(See **WARNINGS: Proteinuria, DOSAGE AND ADMINISTRATION: Dose Modifications**, and **PRECAUTIONS: Geriatric Use.)**

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving AVASTIN has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with AVASTIN, primarily in combination with chemotherapy. High titer human anti-AVASTIN antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AVASTIN with the incidence of antibodies to other products may be misleading.

Metastatic Carcinoma of the Colon and Rectum

The data in Tables 4 and 5 were obtained in Study 1. All NCI-CTC Grade 3 and 4 adverse events and selected NCI-CTC Grade 1 and 2 adverse events (hypertension, proteinuria, thromboembolic events) were reported for the overall study population. The median age was 60, 60% were male, 79% were Caucasian, 78% had a colon primary lesion, 56% had extra abdominal disease, 29% had prior adjuvant or neoadjuvant chemotherapy, and 57% had ECOG performance status of 0. The median duration of exposure to AVASTIN was 8 months in Arm 2 and 7 months in Arm 3. Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events, which occurred at a higher incidence ($\geq 2\%$) in patients receiving bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are presented in Table 4.

Table 4
NCI-CTC Grade 3 and 4 Adverse Events in Study 1
(Occurring at Higher Incidence (≥2%) AVASTIN vs. Control)

	Arm 1 IFL+Placebo (n=396)	Arm 2 IFL+AVASTIN (n=392)
NCI-CTC Grade 3–4 Events	295 (74%)	340 (87%)
Body as a Whole		
Asthenia	28 (7%)	38 (10%)
Abdominal Pain	20 (5%)	32 (8%)
Pain	21 (5%)	30 (8%)
Cardiovascular		
Hypertension	10 (2%)	46 (12%)
Deep Vein Thrombosis	19 (5%)	34 (9%)
Intra-Abdominal Thrombosis	5 (1%)	13 (3%)
Syncope	4 (1%)	11 (3%)
Digestive		
Diarrhea	99 (25%)	133 (34%)
Constipation	9 (2%)	14 (4%)
Hemic/Lymphatic		
Leukopenia	122 (31%)	145 (37%)
Neutropenia[a]	41 (14%)	58 (21%)

[a] Central laboratories were collected on Days 1 and 21 of each cycle.
Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

NCI-CTC Grade 1–4 adverse events which occurred at a higher incidence (≥5%) in patients receiving bolus-IFL plus AVASTIN as compared to the bolus-IFL plus placebo arm, are presented in Table 5.

Table 5

NCI-CTC Grade 1–4 Adverse Events in Study 1
(Occurring at Higher Incidence (≥5%) in IFL + AVASTIN vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+AVASTIN (n=102)	Arm 3 5-FU/LV+AVASTIN (n=109)
Body as a Whole			
Pain	54 (55%)	62 (61%)	67 (62%)
Abdominal Pain	54 (55%)	62 (61%)	55 (50%)
Headache	19 (19%)	27 (26%)	30 (26%)
Cardiovascular			
Hypertension	14 (14%)	23 (23%)	37 (34%)
Hypotension	7 (7%)	15 (15%)	8 (7%)
Deep Vein Thrombosis	3 (3%)	9 (9%)	6 (6%)
Digestive			
Vomiting	46 (47%)	53 (52%)	51 (47%)
Anorexia	29 (30%)	44 (43%)	38 (35%)
Constipation	28 (29%)	41 (40%)	32 (29%)
Stomatitis	18 (18%)	33 (32%)	33 (30%)
Dyspepsia	15 (15%)	25 (24%)	19 (17%)
GI Hemorrhage	6 (6%)	25 (24%)	21 (19%)
Weight Loss	10 (10%)	15 (15%)	18 (16%)
Dry Mouth	2 (2%)	7 (7%)	4 (4%)
Colitis	1 (1%)	6 (6%)	1 (1%)
Hemic/Lymphatic			
Thrombocytopenia	0	5 (5%)	5 (5%)
Nervous			
Dizziness	20 (20%)	27 (26%)	21 (19%)

Table 5 (cont'd)
NCI-CTC Grade 1–4 Adverse Events in Study 1

(Occurring at Higher Incidence (≥5%) in IFL + AVASTIN vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+AVASTIN (n=102)	Arm 3 5-FU/LV+AVASTIN (n=109)
Respiratory			
Upper Respiratory Infection	38 (39%)	48 (47%)	44 (40%)
Epistaxis	10 (10%)	36 (35%)	35 (32%)
Dyspnea	15 (15%)	26 (26%)	27 (25%)
Voice Alteration	2 (2%)	9 (9%)	6 (6%)
Skin/Appendages			
Alopecia	25 (26%)	33 (32%)	6 (6%)
Skin Ulcer	1 (1%)	6 (6%)	7 (6%)
Special Senses			
Taste Disorder	9 (9%)	14 (14%)	23 (21%)
Urogenital			
Proteinuria	24 (24%)	37 (36%)	39 (36%)

The data in Table 6 were obtained in Study 3. Only NCI-CTC Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment were reported. The median age was a 61 years, 40% were female, 87% were Caucasian, 99% received prior chemotherapy for metastatic colorectal cancer, 26% had received prior radiation therapy, and the 49% had an ECOG performance status of 0. Selected NCI-CTC Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events which occurred at a higher incidence in patients receiving FOLFOX4 plus AVASTIN as compared to those who received FOLFOX4 alone, are presented in Table 6. These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 3.

Table 6
NCI-CTC Grade 3–5 Non-Hematologic and
Grade 4–5 Hematologic Adverse Events in Study 3
(Occurring at Higher Incidence (≥2%)
with AVASTIN + FOLFOX4 vs FOLFOX4)

	FOLFOX4 (n=285)	FOLFOX4 + AVASTIN (n=287)	AVASTIN (n=234)
Patients with at least one event	171 (60%)	219 (76%)	87 (37%)
Gastrointestinal			
Diarrhea	36 (13%)	51 (18%)	5 (2%)
Nausea	13 (5%)	35 (12%)	14 (6%)
Vomiting	11 (4%)	32 (11%)	15 (6%)
Dehydration	14 (5%)	29 (10%)	15 (6%)
Ileus	4 (1%)	10 (4%)	11 (5%)
Neurology			
Neuropathy–sensory	26 (9%)	48 (17%)	2 (1%)
Neurologic–other	8 (3%)	15 (5%)	3 (1%)
Constitutional symptoms			
Fatigue	37 (13%)	56 (19%)	12 (5%)
Pain			
Abdominal pain	13 (5%)	24 (8%)	19 (8%)
Headache	0 (0%)	8 (3%)	4 (2%)
Cardiovascular (general)			
Hypertension	5 (2%)	26 (9%)	19 (8%)
Hemorrhage			
Hemorrhage	2 (1%)	15 (5%)	9 (4%)

Non-Squamous, Non–Small Cell Lung Cancer

The data in Table 7 were obtained in Study 5. Only NCI-CTC Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were reported. The median age was 63, 46% were female, no patients had received prior chemotherapy, 76% had Stage IV disease, 12% had Stage IIIB disease with malignant pleural effusion, 11% had recurrent disease, and 40% had an ECOG performance status of 0. The median duration of exposure to AVASTIN was 4.9 months.

NCI-CTC Grade 3, 4, and 5 adverse events that occurred at a ≥2% higher incidence in patients receiving PC plus AVASTIN as compared with PC alone are presented in Table 7.

Table 7
NCI-CTC Grade 3–5 Non-Hematologic and
Grade 4 and 5 Hematologic Adverse Events in Study 5
(Occurring at a ≥2% Higher Incidence in
AVASTIN-Treated Patients Compared with Control)

NCI-CTC Category Term[a]	No. (%) of NSCLC Patients	
	PC (n=441)	PC + AVASTIN (n=427)

Any event	286 (65%)	334 (78%)
Blood/bone marrow		
Neutropenia	76 (17%)	113 (27%)
Constitutional symptoms		
Fatigue	57 (13%)	67 (16%)
Cardiovascular (general)		
Hypertension	3 (0.7%)	33 (8%)
Vascular		
Venous thrombus/embolism	14 (3%)	23 (5%)
Infection/febrile neutropenia		
Infection without neutropenia	12 (3%)	30 (7%)
Infection with NCI-CTC Grade 3 or 4 neutropenia	9 (2%)	19 (4%)
Febrile neutropenia	8 (2%)	23 (5%)
Pulmonary/upper respiratory		
Pneumonitis/pulmonary infiltrates	11 (3%)	21 (5%)
Metabolic/laboratory		
Hyponatremia	5 (1%)	16 (4%)
Pain		
Headache	2 (0.5%)	13 (3%)
Renal/genitourinary		
Proteinuria	0 (0%)	13 (3%)

PC=paclitaxel/carboplatin.

Events were sorted by highest relative frequency across all treatment arms combined.

[a] Events were reported and graded according to NCI-CTC, Version 2.0. Per protocol, investigators were required to report NCI-CTC Grade 3–5 non-hematologic and Grade 4 and 5 hematologic events.

Other Serious Adverse Events

1. The following additional serious adverse events occurred in at least one subject treated with AVASTIN in clinical studies or post-marketing experience:

a. *Body as a Whole: polyserositis*

b. *Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic ulceration*

c. *Hemic and lymphatic: pancytopenia*

d. *Respiratory: nasal septum perforation*

OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

DOSAGE AND ADMINISTRATION

Do not initiate AVASTIN until at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of AVASTIN.

Metastatic Carcinoma of the Colon or Rectum

AVASTIN, used in combination with intravenous 5-FU-based chemotherapy, is administered as an intravenous infusion (5 mg/kg or 10 mg/kg) every 14 days.

The recommended dose of AVASTIN, when used in combination with bolus-IFL, is 5 mg/kg.

The recommended dose of AVASTIN, when used in combination with FOLFOX4, is 10 mg/kg.

Non-Squamous, Non–Small Cell Lung Cancer

The recommended dose of AVASTIN is 15 mg/kg, as an IV infusion every 3 weeks.

Dose Modifications

There are no recommended dose reductions for the use of AVASTIN. If needed, AVASTIN should be either discontinued or temporarily suspended as described below.

AVASTIN should be permanently discontinued in patients who develop gastrointestinal perforation, wound dehiscence requiring medical intervention, serious bleeding, a severe arterial thromboembolic event, nephrotic syndrome, hypertensive crisis or hypertensive encephalopathy. In patients developing RPLS, discontinue AVASTIN and initiate treatment of hypertension, if present. (See **WARNINGS: Reversible Posterior Leukoencephalopathy Syndrome.)**

Temporary suspension of AVASTIN is recommended in patients with evidence of moderate to severe proteinuria pending further evaluation and in patients with severe hypertension that is not controlled with medical management. The risk of continuation or temporary suspension of AVASTIN in patients with moderate to severe proteinuria is unknown.

AVASTIN should be suspended at least several weeks prior to elective surgery. (See **WARNINGS: Gastrointestinal Perforation** and **Wound Healing Complications** and **PRECAUTIONS: Surgery.)** AVASTIN should not be resumed until the surgical incision is fully healed.

Preparation for Administration

AVASTIN should be diluted for infusion by a healthcare professional using aseptic technique. Withdraw the necessary amount of AVASTIN to obtain the required dose and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Diluted AVASTIN solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for up to 8 hours. No incompatibilities between AVASTIN and polyvinylchloride or polyolefin bags have been observed.

AVASTIN infusions should not be administered or mixed with dextrose solutions.

Administration

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. The initial AVASTIN dose should be delivered over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Stability and Storage

AVASTIN vials must be refrigerated at 2–8°C (36–46°F). AVASTIN vials should be protected from light. Store in the original carton until time of use. **DO NOT FREEZE. DO NOT SHAKE.**

HOW SUPPLIED

AVASTIN is supplied as 4 mL and 16 mL of a sterile solution in single-use glass vials to deliver 100 and 400 mg of Bevacizumab per vial, respectively.

Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN (25 mg/mL).
NDC 50242-060-01

Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN (25 mg/mL).
NDC 50242-061-01

REFERENCES

2. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997;57:4593-9.

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e. **AVASTIN®**
(Bevacizumab)

f. **For Intravenous Use**

g. Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

7455XXX
LV0XXX
48XXXXX
Initial U.S.Approval: February 2004
Code Revision Date: October 2006

10/11/06

Jeff Summers, Clinical Reviewer, DBOP, date

10/11/06

Joseph Gootenberg, Team Leader, DBOP, date

Medical Officer's Consultative Review Memorandum

BLA:	125085/85
Sponsor:	Genentech
Product:	Bevacizumab (Avastin)
Consultant:	Jeff Summers, MD, OODP/DBOP
Reviewer:	Barbara A. Stinson, DO, DMIHP BAS
Through:	Dwaine Rieves, MD, Deputy Director, DMIHP George Mills, Director, DMIHP
Today's date:	August 8, 2006

Dwaine Rieves for GM 8-8-06

I. Overview:

This consultation was requested to review the Independent Radiology Review Charter (IRC) submitted for an audit of a phase 2/3 clinical protocol titled " Randomized Phase II/III Trial of Paclitaxel plus Carboplatin With or Without Bevacizumab in Patients with Advanced NSCLC." The drug is currently under review for a new indication: first line treatment of patients with locally advanced, metastatic or recurrent NSCLC in combination with platinum containing regimens. The sponsor, Genentech, has contracted — to provide a retrospective independent confirmation of the selected CT and MRI exams for selected subjects that were enrolled in this study. b(4)

The study performed was an open-label, randomized, multicenter study. Subjects were randomized in a 1:1 ratio to therapy consisting of either:

- Arm A: Paclitaxel + Carboplatin or
- Arm B: Paclitaxel + Carboplatin + Bevacizumab.

Each cycle was repeated every 6 weeks for a total of 6 cycles. After the 6 cycles, subjects who did not progress on the Bevacizumab were continued on the drug every 3 weeks until progressive disease or unacceptable toxicity.

The primary objective was overall survival. The secondary objectives were response rate and time to progression.

The tumor assessment schedule for imaging is duplicated below, (explanation of notations taken from the — Procedures Document, page 17, dated 17Jul2006). b(4)

Exam	Pre-Study (Within 4 Weeks before Randomization)	Week 7	Week 13	Arm B (Bevacizumab Alone) Day of Treatment	End of Treatment
Tumor Assessment[1]	R	R	R	R[2]	R[3]

R: Required. "Scans or X-Rays" were required to document measurable and nonmeasurable disease.
[1]: The protocol states that the same imaging modality must be used throughout the study for measurement of target and non-target lesions for each subject.
[2]: Every third cycle
[3]: Performed every 3 months until progression
[4]: Follow-up after subject discontinues protocol therapy for subjects < 2 years from study entry, every 6 months if subject is 2-5 years from study entry. No specific requirements if subject is > 5 years from entry.

II. FDA DMIHP Consultant's findings:

The review team from DBOP has asked the consultant to review the submitted Independent Radiology Review Procedures Document. We have the following comments for the DBOP team to consider in review of the Procedures Document.

Overall, the Document describes acceptable plans for review of selected images. The items listed below are optional considerations for you to consider conveying to the sponsor in order to enhance the Document's clarity.

1. Appendix B, Management of Markings/Measurements/Annotations, notes that films and media coming to — for review may have marks from prior interpretations and notes an action to be taken by a radiologist when Image Quality Assessment (IQA) is performed. The planned actions are acceptable. Although the Document's text does not suggest that the independent radiologic readers would perform image quality assessment, the Document could avoid any question by explicitly stating that these readers will not perform image quality assessment. b(4)

2. Section 4.4.1 notes that in the event that sites send imaging studies to — that have been performed but that are not identified in the Genentech database, the scans will be included in the —— review. In order to avoid any confusion regarding the specific patients to be audited, the Document's Section 4.4.1 text could be improved by noting that only the images "from the selected patients for audit" will be reviewed. b(4)

3. It may be helpful to develop and include timeframes for the workflow process, for example to note time to resolve a query, batch readings, reading within a certain timeframe of image receipt, and identify the time frame applicable to the designation of a significant delay in the submission process.

III. Summary of Independent Radiology Review Process

IMAGING HANDLING

9 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125085/85

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Medical Division: Biologic Oncology Drug Products (HFD-107)
Biometrics Division: Division V, Office of Biostatistics (HFD-711)

STATISTICAL KEY WORDS:	**Log-rank statistic; Cox's regression model**
BLA NUMBER:	**BLA125085 / 85** 9-25-06
DRUG NAME:	**Avastin™ (Bevacizumab)**
INDICATION:	**Non-Small Cell Lung Cancer**
SPONSOR:	**Genentech, Inc.**
STATISTICAL REVIEWER:	**Yuan-Li Shen, Dr. P.H. (HFD-711)**
STATISTICAL TEAM LEADER: Division of Biometrics V	**Mark Rothmann, Ph.D. (HFD-711)**
DIRECTOR:	**Aloka Chakravarty, Ph.D. (HFD-711)**
CLINICAL REVIEWERS:	**Jeff Summers, M.D. (HFD-107)**
CLINICAL TEAM LEADER:	**Joe Gootenberg, M.D. (HFD-107),**
PROJECT MANAGER:	**Sharon Sickafuse (HFD-107)**

Distribution: BLA 125085
HFD-107/ Gootenberg, Keegan, Sickafuse, Summers
HFD-711/Chakravarty, Rothmann, Shen
HFD-700/O'Neill, Patrician

File directory:
C:/BLA_2006/Bevacizumab/Bevacizumab_NSCLC_statreview_2006.doc

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List of Figures

1 Executive Summary of Statistical Findings

The sponsor, Genentech, Inc., is seeking supplemental labeling claims of Avastin® in combination with paclitaxel and carboplatin for treatment of advanced and metastatic non-small-cell lung cancer (NSCLC) in patients who did not previously receive chemotherapy. This review provides a summary of the clinical efficacy results, statistical issues and an overview of the studies submitted in this application.

1.1 Recommendations and Conclusions

Based on the Phase II/III (study E4599), open-label, randomized, controlled study results, the Bev+paclitaxel+carboplatin arm demonstrates a significant improvement of overall survival as compared with paclitaxel+carboplatin alone arm (median survival times were 12.3 months versus 10.3 months, respectively). The beneficial treatment effect in Bev+paclitaxel+carboplatin arm on overall survival was consistently shown in various subgroups defined by measurable disease, prior radiation therapy, ECOG performance status at study entry, race and tumor burden. There was a lack of internal consistency in the estimated effect for gender, age and weight change subgroups. The beneficial treatment effect was not clear in female (hazard ratio=0.99, 95% C.I.=[0.79, 1.25]), patients aged 65 years or older (hazard ratio=0.91, 95% C.I.=[0.72, 1.14]), patients with baseline weight loss of 5% or greater in the 6 months prior to enrollment (hazard ratio=0.96, 95% C.I.=[0.73, 1.26]) or histologic subtypes other than adenocarcinoma (although many categories had small cell sizes).

Since imaging data was not collected based on standard procedure and different tumor assessment schedules between arms, the results of progression free survival or objective response should be interpreted with caution.

1.2 Brief Overview of Clinical Studies

Genentech submitted a Phase II/III, open-label, randomized, active-controlled, multicenter study (study E4599) to evaluate Avastin® (bevacizumab) combined with paclitaxel and carboplatin as first-line treatment for patients with locally advanced or metastatic NSCLC. The sponsor also submit a phase II , multidose, randomized,

multicenter study to evaluate Avastin® (bevacizumab) combined with paclitaxel and carboplatin chemotherapy in patients with locally advanced or metastatic (Stage IIIB or IV) NSCLC. This review will mainly focus on study E4599.
These studies were submitted to support the following proposed claim :

- AVASTIN, in combination with platinum-based chemotherapy, is indicated for first-line treatment of patients with locally advanced, metastatic, or recurrent non–small cell lung cancer other than predominant squamous histology.

Study E4599 was a multicenter, Phase II/III, randomized, open-label, active controlled trial to evaluate the efficacy and safety of bevacizumab given in combination with carboplatin/paclitaxel chemotherapy to patients with locally advanced or metastatic NSCLC other than squamous-cell carcinoma as categorized by the predominant cell type.

This trial was conducted in the United States by the Eastern Cooperative Oncology Group (ECOG) in collaboration with the cooperative groups according to their respective SOPs for trial monitoring, data flow, and adverse event monitoring.

Eligible patients had measurable, histologically confirmed, advanced or metastatic NSCLC (stage IIIB with malignant pleural effusion, or stage IV or recurrent disease). Patients were randomized to the following two arms in a 1:1 ratio : carboplatin/paclitaxel (CP arm) and bevacizumab+carboplatin/paclitaxel (BV+CP arm). A stratified randomization scheme was used based on the presence of measurable disease, prior receipt of radiation therapy, degree of weight loss and disease stage.

The primary endpoint of this study is overall survival and the secondary efficacy endpoints include progression-free survival, objective response and duration of objective response. The primary comparison was between two treatment arms using a stratified log-rank test.

1.3 Statistical Issues and Findings

The primary efficacy result based on overall survival from study E4599 is significant in favor of BV/CP arm. The median survival times are 10.3 months (95% C.I.=[9.36, 11.73]) and 12.3 months (95% C.I.=[11.30,13.73]) for CP alone arm and BV/CP arm, respectively.

There are a few statistical issues related to the analysis:

- The sponsor shows significant survival benefit in the BV/CP arm as compared with CP arm alone. However, several issues were noted for the overall survival results:
    a. Only one trial was submitted to support the NSCLC indication.
    b. Lack of internal consistency of the results where the treatment effect is not clear in several patient subgroups (see section 4.1 for further details).
- It is noted that the sponsor's stated schedules of tumor evaluation were not strictly followed and there were more unscheduled visits occurred for the CP alone arm compared with those of the BV/CP arm. The magnitude and direction of the bias introduced by the differential timing of tumor assessment can not be determined based on the data submitted.
- In the sponsor's analysis of PFS, the planned censoring scheme may lead to informative censoring that may result in a biased estimate of the treatment effect for PFS endpoint.
- Due to different adverse event reporting requirement and different source of data collection, the adverse event results can not be confirmed.
- Several data collection/database quality issues were identified. For example, the stratification factor data collected based on ECOG eligibility form are not consistent with the data collected from the CRF pages.

2 Introduction

This section provides an overview of the submitted trials.

2.1 Overview

This subsection provides a background of the design of the submitted trial, the data analyzed and the source, and any major statistical issues.

2.1.1 Background

Genentech submitted the results from a multicenter, open-label, Phase II/III randomized trial of bevacizumab + carboplatin/paclitaxel chemotherapy versus carboplatin/paclitaxel chemotherapy alone in patients with locally advanced or metastatic NSCLC other than squamous-cell carcinoma. A stratified randomization scheme was used for this study.

The primary efficacy endpoint of this trial is overall survival and the secondary efficacy endpoints include progression-free survival, objective response and duration of objective response. The primary comparisons for time-to-event endpoints between chemotherapy alone arm and bevacizumab + chemotherapy arm are based on a stratified log-rank test.

This is a trial conducted by the cooperative groups, Genentech is not involved in the conduct of the trial.

2.1.2 Major Statistical Issues

Several statistical issues with respect to the analysis are summarized below:

- The sponsor shows significant survival benefit in the BV/CP arm as compared with CP arm alone. However, several issues were noted for the overall survival results:
    a. Only one trial was submitted to support the NSCLC indication.
    b. Some subgroup analyses did not show survival benefit (e.g. female, patients age $\geq$ 65 years old, patients with baseline weight loss $\geq$ 5 % in the 6 months prior to enrollment and histological subtypes other than adenocarcinoma). Therefore, the lack of internal consistency is the an issue.

- It is noted that the planned frequency of tumor assessment post chemotherapy is not

consistent between treatment arms. The differential tumor assessment schedules between arms may result in ascertainment bias in PFS. Based on this reviewer's observation, the sponsor's stated schedules of tumor evaluation was not strictly followed and there were more unscheduled visits occurred for the CP alone arm compared with those of the BV/CP arm. The magnitude and direction of the bias introduced by the differential timing of tumor assessment can not be determined based on the data submitted.

- In the sponsor's analysis of PFS, patients who took non-protocol specified anti-tumor therapy were censored at the last tumor assessment prior to the non-protocol specified anti-tumor therapy. It is noted that this censoring scheme may be informative censoring and lead to estimates that do not unbiasedly estimate the parameters of the PFS.
- Due to different adverse event reporting requirement and different source of data collection, the adverse event results can not be confirmed.
- Several data collection/database quality issues were identified. For example, the stratification factor data collected based on ECOG eligibility form are not consistent with the data collected from the CRF pages.

2.2 Data Sources

Data used for review is from the electronic submission received on 4/10/06. The network path is in \\Cbsap58\m\EDR Submissions\2006 BLA\DCC60002776\blamain\crt\datasets\E4599.

3 Statistical Evaluation

The efficacy analysis results will be presented in this section for protocols E4599.

3.1 Evaluation of Efficacy

3.1.1 Introduction

This study was a multicenter, Phase II/III Trial of bevacizumab + carboplatin/paclitaxel chemotherapy versus carboplatin/paclitaxel chemotherapy alone in previously with

locally advanced or metastatic NSCLC. Advanced NSCLC is defined as Stage IIIb with malignant pleural effusion, Stage IV, or recurrent disease. Patients must have histologically or cytologically confirmed non-small cell lung cancer, except squamous-cell carcinoma. Patients also must have measurable or non-measurable disease and ECOG performance status of 0 or 1. Prior or current use of systemic chemotherapy was not allowed. Immunotherapy, hormonal therapy, or radiotherapy within 3 weeks prior to randomization was also not allowed.

This trial is conducted in the United States by the Eastern Cooperative Oncology Group (ECOG) in collaboration with the cooperative group Cancer and Leukemia Group (CALGB), Southwest Oncology Group (SWOG), National Surgical Adjuvant Breast and Bowel Project (NSABP), North Central Cancer Treatment Group (NCCTG), and Radiation Therapy Oncology Group (RTOG) according to their respective SOPs. Genentech is not involved in the conduct of the trial.

Eligible patients were randomized to the following three arms in a 1:1 ratio:

- Arm A: carboplatin/paclitaxel chemotherapy (CP arm)
- Arm B: bevacizumab + carboplatin/paclitaxel chemotherapy (BV/CP arm)

Patients in both arms received chemotherapy on day 1 of each of six 3-week cycles for 6 cycles or until disease progression. All patients received chemotherapy in the order shown below (Arm B patients received bevacizumab immediately after carboplatin):

Table 1 Sponsor's Summary of Treatment Regimen

Arm/Agent	Dose	Administration	Treatment Day
CP			
Paclitaxel	200 mg/m^2	IV infusion over 3 hours	Day 1
Carboplatin	AUC = 6.0 [a]	IV infusion over 15–30 minutes	Day 1
BV/CP			
Paclitaxel	200 mg/m^2	IV infusion over 3 hours IV infusion	Day 1
Carboplatin	AUC = 6.0 [a]	over 15–30 minutes IV infusion	Day 1
Bevacizumab	15 mg/kg	over 90 minutes [b]	Day 1

AUC = area under the concentration–time curve; IV = intravenous.

Note: Treatment regimens are repeated every cycle (3 weeks). Dose calculations are based on actual body weight at the beginning of each cycle.

[a] Dose based on the Calvert formula with AUC = 6.0 mg/mL × min.

[b] The initial dose is administered over a minimum of 90 minutes. Assuming no adverse reactions, the second dose is administered over a minimum of 60 minutes and third and subsequent doses are administered over a minimum of 30 minutes.

Bevacizumab was given immediately after carboplatin administration. Upon completing six cycles of chemotherapy, patients in arm B who experienced a complete response (CR), partial response (PR), or stable disease (SD) without PD (progressive disease) continued to receive bevacizumab 15 mg/kg IV every 3 weeks until PD or unacceptable toxicity. Patients in either arm were required to discontinue treatment upon PD.

Stratified randomization was performed based on the following stratification factors:

- Measurable disease (yes vs. no);
- Prior radiation therapy (yes, vs. no);
- Degree of weight loss over the previous 6 months (<5% vs. ≥5%);
- Disease stage (stage IIIb with pleural effusion vs. stage IV vs. recurrent).

Based on the protocol, the objectives of the trial were summarized as follows:

- To assess overall survival in patients with advanced or metastatic (stage IIIB-

pleural effusion/IV), nonsquamous histology NSCLC treated with carboplatin plus paclitaxel ± bevacizumab.

- To assess response rates, time to progression, and toxicity in patients with advanced or metastatic (stage IIIB-pleural effusion/IV), nonsquamous histology NSCLC treated with carboplatin plus paclitaxel ± bevacizumab.

For regulatory submission purpose, Genentech specified the following primary objectives on the July 29, 2004 (finalized on September 29, 2004) statistical analysis plan (SAP) :

- To assess overall survival in patients with previously untreated locally advanced or metastatic (Stage IIIb with malignant pleural effusion or Stage IV or recurrent) NSCLC (excluding NSCLC categorized as squamous cell) treated with carboplatin/paclitaxel ± bevacizumab.

The secondary objective as stated in the SAP was

- To assess objective response rate, PFS, and toxicity in patients with previously untreated locally advanced or metastatic (Stage IIIb with malignant pleural effusion or Stage IV or recurrent) NSCLC (excluding NSCLC categorized as squamous cell) treated with bevacizumab ± carboplatin/paclitaxel.

Overall tumor burden was evaluated by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST). Tumor evaluations for both arms were performed every two cycles (6 weeks) during the chemotherapy administration period (i.e., scheduled for baseline, weeks 7 and 13). The interval between post-chemotherapy tumor assessments differed between treatment arms. Based on protocol, additional tumor evaluations in CP arm are conducted at the end of chemotherapy (week 19) and every 3 months (12 weeks) thereafter until disease progression or death. Post-chemotherapy tumor evaluations in BV/CP arm were scheduled for every third cycle of bevacizumab (i.e. every 9 weeks), starting with Week 28 and continuing until disease progression or death. CR and PR were confirmed $\geq$ 4 weeks after the criteria for response were first met.

Adverse event (AE) report schedule was different between treatment arms due to respective duration of protocol-specified therapy. All patients had AE evaluated every cycle for the first six cycles. While on treatment, patients in the BV/CP arm had AE collected every three cycles after the first six cycles. For both arms, after treatment discontinuation, adverse events were collected every 3 months for 0–2 years and every 6 months for 2–5 years if the patient experienced (prior to diagnosis of recurrence or second primary) any severe (Grade $\geq$ 3) long-term toxicity that had not been previously reported.

AE report methods were also different between treatment arms. In general, the E4599 Adverse Event/Toxicity Form was used to collect data on specific AE and their relationship to treatment. Listed toxicities included grade 4 and 5 hematologic events and grade 3-5 non-hematologic events. Adverse events were also collected via expedited reporting which is different between treatment arms. In Arm A, the expedited AE reporting use the MedWatch system, while in Arm B, the NCI's Adverse Expedited Reporting System (AdEERS) was used.

In addition, the required reporting of adverse events through expedited reporting system are different between treatment arms. The ECOG statistician indicates in the Report on the Second Interim Analysis of E4599 that because of the differences in reporting requirements, formal inferences comparing the rates are not generally possible for the data from the expedited reports.

The numbers of patients randomized, treated and early discontinued of study medication were summarized in the following table:

Table 2 Summary of the Number of Patients

Study	Duration	Population	CP	BV/CP
E4599	07/19/01-4/07/04 (enrollement completed)	Randomized	444	434
		Not Treated	3(0.7%)	7 (1.6%)
	Study completion occurred on Dec. 30, 2005 (date of ECOG database transfer)	Safety population [a]	441 (99.3%)	427 (98.4%)
		Protocol therapy [b] discontinuation	256 (57.7%)	421(97.0%)

[a] Safety population defined as all randomized patients who receive study treatment (i.e. at least one full or partial dose of any of the three study drugs:bevacizumab, carboplatin, or paclitaxel).

Note : This is based on ECOG data transfer on Dec. 30, 2005.

[b] For comparability of protocol therapy discontinuation between treatment arms, please see the reviewer's comments from the table for Patient Disposition and Reasons of Discontinuation of Study Therapy.

At the time of the first patient enrolled (July 29, 2001), the study was conducted based on the original protocol. Note original protocol was not available at ECOG. There were several amendments to the protocol occurred on

- Amendment 1 August 8, 2002;
- Amendment 2, January 29, 2003;
- Amendment 3 and 4 : August 28, 2003 ;
- Amendment 5 : December 30, 2003;
- Amendment 6: January 29. 2004;
- Amendment 7: August 13, 2004
- Amendment 8: January 26, 2005;
- Amendment 9: August 23, 2005.

Most of the amendments were either related to safety evaluation or were administrative. The amendments that may affect the efficacy evaluation include:

- Amendment 1 (August 8, 2002) :
  1. Weight loss stratification factor was corrected.
     (reviewer's comment: the revised version is stated as baseline weight loss < 5% vs. ≥ 5%. However, it is not clear what is the original version.)
  2. Change patient population: exclude patients who presented with gross hemoptysis at study entry from enrolling in the trial.

- Amendment 4 (August 28, 2003): the statistical section was rewritten to remove a scheduled suspension as recommended by the ECOG DMC on April 22, 2003.

- Amendment 6 (November 5, 2003): The statistical consideration section was updated to account for expanded accrual. The planned enrollment was increased from 640 to 842 total patients. The sponsor modified the monitoring plan to provide adequate power for smaller treatment difference than in the original design.

Two interim analyses and one final analysis were performed. The projected interim analysis times corresponds to 44% (286 deaths) and 70% (455 deaths) information level with the targeted final evaluation at 650 deaths for CP vs. BV/CP comparison.

The interim analyses were based on repeated confidence intervals (RCI, described by Jennison and Turnbull, 1989) for the hazard ratio (CP vs. BV/CP), using the O'Brien-Fleming stopping boundaries based on Lan and DeMets α-spending function, controlling for a 1-sided 0.025 significance level. If at any interim analysis, the lower bound of the confidence interval for the survival hazard ratio exceeds 1, the null hypothesis of equal survival will be rejected in favor of the alternative that the survival is superior in the BV/CP arm. This procedure is asymptotically equivalent to stopping when the logrank test crossed the O'Brien-Fleming boundary. Also, if at any interim analysis, the upper bound of the repeated confidence interval is smaller than 1.25, then the study will be stopped in favor of the null hypothesis.

Reviewer's comments:

To be consistent with the Genentech's primary analysis, the stopping boundaries will be based on the hazard ratio of BV/CP vs. CP for later discussion of interim analysis results. If the upper bound of the confidence interval for the hazard ratio is lower than 1, the null hypothesis of equal survival will be rejected and the if the lower bound of the

repeated confidence interval is greater than 0.8, then the study will be stopped in favor of the null hypothesis.

Based on the protocol, the study was monitored by the ECOG DMC at bi-annual meetings. The ECOG DMC reviewed the study for safety, progress, and when appropriate, interim analyses of outcome data. The DMC meetings occurred on April 3, 2002, October 30, 2002, April 22, 2003, November 5, 2003, April 27, 2004 and November 2, 2004 and on a special conference call held on March 9, 2005. The DMC also met by correspondence during late June and early July 2002.

The sponsor did not submit the DMC meeting minutes for most of the meetings except the second interim analysis report (written by ECOG statistician, dated March 9, 2005) and a summary of ECOG DMC activities produced by Genentech. In these reports, the monitoring history was highlighted. A summary of the report was shown in the appendix.

Reviewer's comment:

- *The sponsor's summary only document the DMC recommendation. The details that support the conclusions or recommendation for each DMC meeting is not clear.*

The first planned interim analysis was performed on **November 2, 2004** (based on a data cutoff of **September 7, 2004**). A total of 865 (out of 878 patients entered) patients were included in the primary analysis. There were 314 deaths (48% of the planned total information of 650 deaths) in the primary analysis (324 overall). The O'Brien-Fleming critical value was 3.02 (correspond to a two-sided significance level of 0.0025) for this interim analysis. The estimated hazard ratio was 0.79 (BV/CP vs. CP), the repeated confidence interval (RCI) based on the O'Brien –Fleming critical value was (0.56, 1.11) and the nominal 2-sided Wald test p-value was 0.038. Since the RCI contained both the null (1.0) and alternative (0.8) values of the hazard ratio, criteria for stopping were not met at this time. The DMC recommended that this study continued based on the design.

The second efficacy interim analysis was conducted on March 9, 2005 (with data cutoff

date of February 9, 2005). A total of 469 deaths (72.2%) occurred among ECOG eligible patients (a total of 855 eligible patients) at the time of the analysis. There were 246 deaths out of 431 patients and 223 deaths out of 424 patients from CP and BV/CP group, respectively. The O'Brien-Fleming critical value at 72.2% information with a prior analysis at 48% was 2.413 (correspond to a two-sided significance level of 0.016) for this interim analysis. The nominal 2-sided Wald test p-value was 0.0075 and the p-value from the logrank test was 0.0074. The median survival time were 10.2 and 12.5 months for CP and BV/CP arm, respectively. The estimated hazard ratio and RCI were 0.78 and (0.62, 0.98). The upper bound of the RCI was less than 1. Based on this review, the ECOG DMC determined that the pre-specified criteria met for statistical significance for the comparison of chemotherapy+bevacizumab versus chemotherapy alone arm.

The original statistical analysis plan dated July 29, 2004 was amended on September, 29, 2004 based on the agency's recommendation (after a meeting on September 2, 2004). In the study report, the sponsor did not perform the following analyses because of the strong efficacy results:

- Exploratory multivariate modeling of the effect of risk factors on PFS and objective response.
- Sensitivity analysis to assess impact of missing tumor assessments on PFS.

Other analyses that were performed differently from those specified in SAP are summarized by Genentech as follows:

- PFS: Data for patients without disease progression or death at the time of analysis who had no tumor assessments were censored at the time of randomization rather than the time of randomization +1 day.

- PFS: Since patients in the CP arm could only receive treatment until Cycle 6, patients who discontinued study treatment prior to progression were not censored at the end of protocol therapy as stated in the SAP. All progression events that occurred were counted as events regardless of the patient's treatment status.

- Objective response: The 95% confidence interval for response rate was estimated using Fleiss' approximation instead of using normal approximation

given in the SAP.

- Duration of objective response: Since patients in the CP arm could only receive treatment until Cycle 6, the duration of objective response was calculated from date of complete or partial response until date of disease progression or death irrespective of number of days following discontinuation of study treatment.

- Time-to-onset adverse event analyses: Because the exact date of onset was not captured for all adverse events, hazard ratios were not calculated for selected adverse events.

- The age categories for the exploratory analyses were changed from "< 40, 40–65, and > 65 years" to "< 40, 40–64, and ≥ 65 years."

The following analyses were not planned in the SAP but were performed:

- The incidence of Grade 3–5 hemoptysis adverse events of patients enrolled before and after Amendment 1 (which excluded entry of patients who had a history of gross hemoptysis) was performed.

- Non-protocol therapy use both prior to and after progression, protocol deviation treatment summaries, and baseline disease and demographic characteristics were calculated separately for males and females.

Reviewer's note :

- *The statistical analysis plan (SAP) was finalized on September 29,2004, about 1 months prior to the first interim analysis (November 2, 2004, based on data cutoff of September 7, 2004).*
- *Genentech indicates that patients who did not have disease progression or death at the time of analysis and who had no tumor assessments were censored at the time of randomization rather than the time of randomization +1 day. However, based on Genentech's E4599 Data and Analysis Tip sheet and the submitted data for PFS, patients who did not have post-baseline tumor assessments the time to disease progression or death were censored at time of randomization +1 day. Since there was no event at time zero, this did not impact the result.*
- *The result based on Fleiss' approximation is similar to that based on normal approximation.*

3.1.2 Efficacy Endpoints

The primary efficacy endpoint for this study was overall survival defined as time from randomization to death from any cause. Patients who were not known to have died or lost to follow-up at the time of analysis were censored at the date that the patient was last known to be alive.

The secondary efficacy endpoints include objective response, progression free survival, and duration of objective response. These endpoints were defined as follows:

Best Overall response : Definition of overall response is based on the combination of tumor responses in target and non-target lesions, along with the presence or absence of new lesions. Best overall response is the best response recorded from randomization to disease progression. This response is summarized in the following table:

Table 3 Overall Response Definition

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	SD[a]	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; PD = progressive disease; PR = partial response; SD = stable disease. CRs and PRs must be confirmed by repeat assessments ≥ 4 weeks after the criteria for response are first met. SD criteria must be met at least once after study entry at a minimum interval of 8 weeks.

[a] Incomplete response/SD.

Objective Response : defined as the occurrence of a complete response (CR) or partial response (PR) overall response per RECIST, confirmed by repeat assessments performed by the investigator ≥ 4 weeks after the criteria for response are first met.

The date of response is the date of the first occurrence of a CT or PR. Patients who did not meet this criteria as assessed by the ECOG Coordinating Center, including patients who had missing post-baseline tumor assessment, were considered non-responders.

Duration of Objective Response : this is defined for the subset of patients who achieved an objective response which is defined as the duration from the time that the measurement criteria are met for a CR or PR per RECIST (whichever occurred first) to the time of disease progression or death from any cause. Data from patients in the BV/CP arm were censored 30 days following discontinuation of study treatment. Patients who had an objective response and did not experience disease progression or who had not died by the time of analysis will be censored at the time of the last tumor assessment.

Progression-Free Survival (PFS) : Defined as time from randomization to disease progression or death from any cause. Progression of disease is defined as a $\geq$ 20% increase in the sum of the longest diameters of the target lesions, taking as reference the smallest sum of longest diameters recorded since the baseline measurement, or the appearance of one or more new lesions.

Data for patients without disease progression or death at the time of analysis were censored at the time of the last tumor assessment. If no tumor assessments were performed after baseline, the time of progression was set at the time of randomization +1. Patients who received non-protocol-specified therapy prior to experiencing documented disease progression were censored at the time of the last tumor assessment prior to receiving non-protocol-specified therapy. Patients who discontinued early prior to disease progression were censored at the time of the last tumor assessment prior to discontinuation.

Note : Patients in this study who experience toxicity and discontinue study treatment went through disease assessment at intervals different from those patients receiving study treatment. To obtain consistent criteria of evaluation of PFS across treatment arms, data for patients who discontinue all study treatment prior to disease progression will be censored at the time of the last tumor assessment prior to discontinuation.

3.1.3 Sample Size Consideration

Based on the original protocol design, a total of 606 eligible patients (640 total) would be enrolled for a total information of 500 deaths. a total of 660 eligible patients (~ 693 total patients by allowing 5% ineligibility) would be enrolled. This sample size was planned to detect an increase in median survival from 8 months in the control arm to 11 months in the experimental arm with 90% power.

On the **November 5, 2003 ECOG DMC meeting,** the study chair and the ECOG Thoracic Committee requested that the DMC consider modifying the design to provide adequate power for a smaller difference in survival. The rationale of decreasing the target difference was based on the review by Breathnach, et. al. (JCO, 19: 1734-42, 2001), who found that differences in median survival time larger than 2 months were very rare in advanced NSCLC studies. In addition, decreasing of the target percent improvement provides some protection if the control median survival prove to be better than 8 months (which may be possible due to a stricter entry criteria in this study compared to previous studies). Based on these reasons, the sample size was increased to enroll 800 eligible patients (842 total) and the total information to 650 deaths. This sample size provides at least 90% power to detect a 30% improvement in survival or 80% power for detecting a 25% improvement (corresponds to a 2 months difference in median survival if the median for the control group is 8 months, but a 2.5 months difference if the median for the control group is 10 months). The revised design increase the sample size to 800 eligible patients (842 total) and total information to 650 deaths to provide the power requested by the DMC.

3.1.4 Efficacy Analysis Method

The primary efficacy analysis was based on a comparison of the CP vs BV/CP using the log-rank test stratified by measurable disease (yes vs. no), prior radiation therapy (yes vs. no), weight loss in the previous 6 months (<5% vs. $\geq$ 5%), and stage (Stage IIIb with pleural effusion vs. Stage IV vs. recurrent). This analysis will be performed at 2-sided α=0.05 level. Intent-to-treat (ITT) population was used for the primary efficacy analysis.

The Kaplan Meier (K-M) method was used to estimate the median duration of survival

for each treatment arm. The Cox proportional hazards (Cox's PH) model stratified by the stratification factors was used to estimate the hazard ratios.

The interim analysis was based on the O'Brien-Fleming topping boundaries based on Lan and DeMets α-spending function, controlling for a 1-sided 0.025 significance level. The boundary was constructed with a targeted final evaluation at 650 deaths.

A sensitivity analysis was planned to evaluate the effect of loss to follow-up on overall survival. If >5% of patients were lost to follow-up for survival, or if the absolute difference in the proportion of patients lost to follow-up is >5%, the sensitivity analysis was to be performed. A "worst case" analysis was used for the survival endpoint. Patients in the BV/CP arm who were lost to follow-up were considered as deaths and the date of death was set to be their last contact date + 1. Patients from the CP arm who were lost to follow-up had their survival censored at the date of the last contact.

The PFS was analyzed based on the similar statistical methods used for the overall survival. Due to the concern of the differences in assessment schedules in the post-chemotherapy phase that can result in biased results, landmark analysis of PFS was also performed to compare treatment groups for patients in each arm who had not progressed or died by week 13 (the final assessment prior to the divergence of the assessment schedules). An additional comparison for patients who had not died or progressed by week 19.

A sensitivity analysis was planned to evaluate the effect of missing tumor assessments on PFS. Patients who died >3 months after their final tumor assessment (where the final assessment was progression-free) was censored at the time of the final post-baseline tumor assessment. If there was no post-baseline assessment, the patient was censored at the randomization date +1.

Reviewer's comment : The analysis indicated above was not performed.

The objective response rates were compared between CP vs BV/CP based on Cochran-Mantel-Haenszel test stratified by prior radiation therapy (yes vs. no), weight loss in the previous 6 months (<5%, ≥ 5%), and stage (Stage IIIb with pleural effusion vs. Stage IV

vs. recurrent). This analysis included only patients who had measurable disease at baseline. An additional analysis was performed for all randomized patients. This analysis included baseline measurable disease (yes vs. no) as an additional stratification factor. The objective response rate estimate and the 95% confidence interval were presented based on normal approximation to the binomial distribution.

In addition to the analysis of objective response, best overall confirmed response was summarized by treatment arm. This summary includes CR, PR, SD (stable disease) and PD (progressive disease) both for patients with measurable disease at baseline and for all randomized patients. The summary also includes a category for unevaluable patients captured on the ECOG Internal Tumor Response Coding Form.

Since the analysis for duration of objective response was based on non-randomized subset of patients, formal hypothesis testing was not performed. Duration of objective response was estimated using Kaplan-Meier method. Comparisons between treatment arms based on the unstratified log-rank test and Cox regression model with treatment in the model were presented for descriptive purpose.

The effect of demographic and baseline prognostic characteristics on overall survival, PFS and objective response were examined. The following demographic and baseline characteristics were considered : measurable disease (yes, no), prior radiation therapy (yes, no), weight loss in the previous 6 months (<5% vs. $\geq$ 5%), and stage (Stage IIIb with pleural effusion, Stage IV or recurrent), ECOG performance status at study entry (0, $\geq$1), age (<40, 40-64 or $\geq$65 years), sex, race (white, non-white), histologic type and baseline sum of the longest diameters of target lesions.

Subgroup analyses for overall survival and PFS were performed based on these categorical variables. The descriptive summaries consisted of the unstratified hazard ratio and the Kaplan-Meier estimates of median survival time.

In addition, the effect of each baseline variables on duration of survival and PFS was evaluated based on Cox proportional hazards model including treatment and each individual variable in the model. An initial multivariate model including treatment and all variables that were individually significant were evaluated. A final multivariate

model included only the treatment effect and all variables that were significant in the initial multivariate model.

The effect of each of the baseline variables on objective response rate was evaluated using the logistic regression model. Similar modeling strategy as described for the Cox's proportional hazards model was used. First, a logistic regression model with treatment and each individual variable was fitted. Then an initial logistic regression model including treatment and all variables that was individually significant were examined. Finally, the final model excluded variables that were not significant in the initial multivariate model.

Reviewer's comment : The multivariate modeling indicated above was not performed for objective response and PFS.

3.1.5 Sponsor's Results and Statistical Reviewer's Findings/Comments

Genentech's clinical result was based on the most current and complete efficacy data and safety available at the time of analysis :

- The database was provided by ECOG to Genentech (December 30, 2005) which ECOG judged to be valid for inference for this study.
- The AdEERS database was provided to Genentech (December 1, 2005).

Between August 22, 2001 and April 8, 2004, 878 patients with locally advanced or metastatic NSCLC classified as other than squamous-cell carcinoma were randomized (444 to the CP arm and 4334 to the BV/CP arm). A total of 256 centers randomized patients into the study.

A summary of patient disposition and reasons for study treatment discontinuation were provided in the following table.

Approximately 99% of the patients received study treatment. The difference in the percentage of patients completed study treatment per protocol reflects the study design. More patients in CP arm (41.7%) completed study treatment after 6 cycles, while less

patients the BV/CP arm (1.2%) completed study treatment since bevacizumab treatment continued until progression. There were more patients in the BV/CP arm (97%) discontinued protocol therapy than patients in the CP arm (57.7%). Among these patients discontinued protocol therapy, BV/CP arm had higher percentage of patients discontinuing therapy as per protocol (61.3% vs. 34.2%) and higher percentage of patients with premature withdrawal from protocol treatment (27.6% vs. 21.6%). The main reason for discontinuation of therapy as per protocol was disease progression during active treatment (55.1% and 30.4% for BV/CP arm and CP arm, respectively). The main reason for premature withdrawal from protocol therapy is toxicity/side effects/complication (18.9% and 12.8% for BV/CP arm and CP arm, respectively).

Four patients in CP arm and 5 in BV/CP are from Extended Participation Project (EPP).

At the time of data cutoff, all patients were known to discontinue the protocol therapy except 1 in BV/CP arm. Due to different treatment period for the two arms, the comparison of discontinued protocol therapy between the treatment arms may not be fair (because more patients in the BV/CP arm remain in the study). The sponsor also summarized the protocol therapy discontinuation on or before cycle 6 of the chemotherapy (see the reviewer's comment).

Table 4 Sponsor's Summary of Patient Disposition and Reasons of Discontinuation of Study Therapy (Study E4599)

	CP (n=444)	BV/CP (n=434)
Treated	441 (99.3%)	427 (98.4%)
Not known to have discontinued protocol therapy	0 (0.0%)	1 (0.2%)
Treatment completed per protocol	185 (41.7%)	5 (1.2%)
Discontinued protocol therapy	256 (57.7%)	421 (97.0%)
Reason not stated [a]	8 (1.8%)	35 (8.1%)
Discontinued as per protocol	152 (34.2%)	266 (61.3%)
Disease progression during active treatment [b]	135 (30.4%)	239 (55.1%)
Death on study	17 (3.8%)	27 (6.2%)

Premature withdrawal from protocol treatment	96 (21.6%)	120 (27.6%)
Toxicity/side effects/complications [c]	57 (12.8%)	82 (18.9%)
Patient withdrawal or refusal	17 (3.8%)	9 (2.1%)
Alternative therapy	7 (1.6%)	3 (0.7%)
Other complicating disease	4 (0.9%)	1 (0.2%)
Other	11 (2.5%)	25 (5.8%)
Not Treated	3 (0.7%)	7 (1.6%)
Known to have no treatment	2 (0.5%)	5 (1.2%)
Patients with no treatment Information	1 (0.2%)	2 (0.5%)

Notes: Patients in the BV/CP arm were treated until progression or important toxicity, whereas patients in the CP arm were treated for six cycles. Percentages were computed relative to the number of randomized patients.

[a] "Reason not stated" category within the "discontinued protocol therapy" group includes patients who have no discontinuation reason but have indication that the protocol therapy has stopped.

[b] The most common reason for study discontinuation other than treatment completed per protocol on or before Cycle 6 was disease progression (133/440 [30.2%] in the CP arm and 75/429 [17.5%] in the BV/CP arm).

[c] The number of patients who discontinued the study due to toxicity/side effects/complications prior to or at Cycle 6 was 57/440 [13.0%] in the CP arm and 60/419 [14.0%] in the BV/CP arm).

Reviewer's comments:

- *The sponsor's summary of protocol therapy discontinuation was based on ITT population where approximately 42% of the patients in the CP arm had completed treatment per protocol (i.e. 6 cycles of chemotherapy) while only 1.2% of the patients in the BV/CP arm had completed treatment per protocol. The comparison of patient discontinued protocol therapy may not be fair since more patients in BV/CP arm remained in the study and these patients had longer evaluation time of protocol therapy discontinuation. Based on the sponsor's summary of patients who discontinued protocol therapy on or prior to cycle 6,*

the incidences of discontinued protocol therapy seem compatible between treatment arms (254/444=57.2% and 218/434=50.2% for the CP alone arm and BV/CP arm, respectively.).

In addition, the most common reason for study discontinuation other than treatment completed per protocol on or before Cycle 6 was disease progression (133/440 [30.2%] in the CP arm and 75/429 [17.5%] in the BV/CP arm). The number of patients who discontinued the study due to toxicity/side effects/complications prior to or at Cycle 6 was nearly identical in the two arms (57/440 [13.0%] in the CP arm and 60/429 [14.0%] in the BV/CP arm).

Thirty-four out of 444 CP patients (7.7%) and 35 out of 434 BV/CP patients were assessed as ineligible for the study by ECOG staff. The majority of the cases was due to baseline CT scans or laboratories being performed outside of the protocol-specified time windows. Other reasons for ineligibility include completion of prior radiation therapy within the 3-week window before enrollment, disease staging (e.g. malignant pleural effusion not confirmed), and histology. It is noted that the ineligible patients identified were not excluded from analyses based on ITT population.

Table 5 Sponsor's Summary of Ineligible Patients (Study E4599)

	CP (n=444)	BV/CP (n=434)
Ineligible for study	34 (7.7%)	35 (8.1%)

Data for protocol deviation was obtained from ECOG case evaluation form (n=233 and 273 for BV/CP and CP arms, respectively) and ECOG eligibility evaluation form (n=391 and n=405 for BV/CP and CP arms, respectively). Based on the ECOG Case Evaluation Form, 3.9% and 2.9% of the patients had minor protocol deviation for BV/CP and CP arms, respectively. There were no major protocol deviation found based on ECOG Case Evaluation Form. Based on ECOG Eligibility Evaluation Form, 2.6% and 1.7% of the patients were found to have stratification error for BV/CP and CP arms, respectively.

Table 6 Sponsor's Summary of Protocol Deviation and No-Protocol Therapy (Study E4599)

Protocol Deviation	CP (n=444)	BV/CP (n=434)
Number of patients who had ECOG Case Evaluation Forms	273	233
Any major or minor protocol deviation based on ECOG case evaluation form [a]	8 (2.9%)	9 (3.9%)
Any major protocol deviation [a]	0 (0.0%)	0 (0.0%)
Incorrect treatment arm given [a]	0 (0.0%)	0 (0.0%)
Cycle 1 dose differed from protocol by > 10% (any component) [a]	0 (0.0%)	0 (0.0%)
Any minor protocol deviation [a]	8 (2.9%)	9 (3.9%)
Treatment started before registration [a]	1 (0.4%)	0 (0.0%)
Other [a]	7 (2.6%)	9 (3.9%)
Number of patients who had ECOG eligibility evaluation form	405	391
Stratification errors [b]	7 (1.7%)	10 (2.6%)
Number of randomized non-EPP patients	440	429
Non-protocol anti-tumor therapy given prior to disease progression [c]	81 (18.4%)	54 (12.6%)
Chemotherapy	54 (12.3%)	39 (9.1%)
Immunotherapy	5 (1.1%)	1 (0.2%)
Hormone therapy	1 (0.2%)	0 (0.0%)
Radiotherapy	21 (4.8%)	11 (2.6%)
Surgery	1 (0.2%)	3 (0.7%)
Other	9 (2.0%)	3 (0.7%)

[a] Percentage is based on the number of patients who had an ECOG Case Evaluation Form.

[b] Percentage is based on the number of patients who had an ECOG Eligibility Evaluation Form.

[c] Percentage is based on the number of randomized non-EPP (Extended Participation Project) patients.

Note: Non-protocol therapy prior to progression forms were not collected for EPP patients or for patients who did not receive non-protocol therapy.

3.1.5.1 Baseline Characteristics

The following table summarizes the disease characteristics including those factors used for stratification in the randomization. It shows that about 60% of patients with ECOG performance status of 1. Approximately 88% of the patients had stage IV or recurrent events. Over 90% of the patients had measurable disease. More than 70% of the patients had less than 5% body weight loss in previous 6 months.

Table 7 Sponsor's Summary of Disease Characteristics including those used for Stratification of Subjects (Study E4599)

	CP (n=444)	BV/CP (n=434)
ECOG performance status (baseline)		
n	443	431
0	175 (39.5%)	171 (39.7%)
1	268 (60.5%)	260 (60.3%)
Disease stage		
n	443	433
IIIb	56 (12.6%)	52 (12.0%)
IV + Recurrent	387 (87.4%)	381 (88.0%)
IV	345 (77.9%)	324 (74.8%)
Recurrent	42 (9.5%)	57 (13.2%)
Measurable disease		
n	444	433
No	41 (9.2%)	36 (8.3%)
Yes	403 (90.8%)	397 (91.7%)
Body weight loss in previous 6 months		
n	443	428
< 5%	316 (71.3%)	308 (72.0%)

≥ 5%	127 (28.7%)	120 (28.0%)
5 to < 10%	80 (18.1%)	75 (17.5%)
10 to < 20%	37 (8.4%)	34 (7.9%)
≥ 20%	10 (2.3%)	11 (2.6%)

Patients' demographic characteristics, such as gender, age and race are presented in the following table. The distribution of the patient demographic characteristics appears to be balanced across treatment groups. The mean age in this patients population was 62 years old (ranged from 27 to 88 years old). CP arm had about 7-8% more male patients than the BV/CP arm, while BV/CP arm had about 7-8% more female patients than the CP arm. Approximately 87% and 84% of the patients were whites in CP and BV/CP arms, respectively.

Table 8 Sponsor's Summary of Demographic and Baseline Characteristics (Study E4599)

	CP (n=444)	**BV/CP (n=434)**
Age (years)		
n	444	434
Mean (SD)	62.0 (9.8)	62.3 (10.4)
Median	63.0	63.0
Range	32–82	27–88
Age category (years)		
n	444	434
< 40	4 (0.9%)	9 (2.1%)
40-64	246 (55.4%)	240 (55.3%)
≥ 65	194 (43.7%)	185 (42.6%)
Sex		
n	444	434
Male	259 (58.3%)	219 (50.5%)
Female	185 (41.7%)	215 (49.5%)
Race		
n	444	434
Asian	3 (0.7%)	5 (1.2%)
Black	24 (5.4%)	23 (5.3%)

Filipino	1 (0.2%)	0 (0.0%)
Hispanic	8 (1.8%)	9 (2.1%)
Indian (Asian)	0 (0.0%)	1 (0.2%)
Native American	2 (0.5%)	1 (0.2%)
White	387 (87.2%)	366 (84.3%)
Other[a]	19 (4.3%)	29 (6.7%)

[a] : "Other" race includes patient refusal, institutional refusal, other, and unknown.

A summary of prior cancer treatment was provided in the following table. In general, the numbers of patients received prior cancer therapy were similar between arms. Only 9% of the patients in each arm had prior radiotherapy. Approximately 17% and 20% of the patients had prior surgery for CP and BV/CP arms, respectively. No one in the CP arm had prior chemotherapy or systemic therapy, while 0.2% and 0.9% of the patients in the BV/CP arm had prior chemotherapy and prior systemic therapy, respectively.

Table 9 Sponsor's Summary of Prior Cancer Treatment (Study E4599)

	CP (n=444)	BV/CP (n=434)
Prior radiotherapy		
n	444	431
No	403 (90.8%)	392 (91.0%)
Yes	41 (9.2%)	39 (9.0%)
Prior surgery		
n	444	431
No	368 (82.9%)	343 (79.6%)
Yes	76 (17.1%)	88 (20.4%)
Prior chemotherapy		
n	444	431
No	444 (100.0%)	430 (99.8%)
Yes	0 (0.0%)	1 (0.2%)
Prior systemic therapy		
n	444	427
No	444 (100.0%)	423 (99.1%)

Yes	0 (0.0%)	4 (0.9%)

The following table summarizes the baseline tumor assessment. Number of sites involved, sites of organ involvement, pleural effusion, histological type and baseline tumor burden seem to be comparable between treatment groups. The majority of patients (68%-69%) had NSCLC classified as adenocarcinoma. More than 70% of the patients had less than 4 involved metastatic sites. The most frequently involved metastatic sites were mediastinal nodes (51%-53%) and Ipsilateral lung (41%-42%). Approximately 38% of the patients had pleural effusion present in each arm. The mean baseline tumor burden (cm) for patients with measurable disease were 8.5 cm and 9.0 cm for CP and BV/CP arm, respectively.

Table 10 Sponsor's Summary of Baseline Tumor Characteristics (Study E4599)

	CP (n=444)	BV/CP (n=434)
Histological type		
N	422	433
Adenocarcinoma	302 (68.3%)	300 (69.3%)
Squamous	2 (0.5%)	1 (0.2%)
Large cell undifferentiated	30 (6.8%)	18 (4.2%)
Bronchioloalveolar (BAC)	11 (2.5%)	12 (2.8%)
NSCLC, NOS	86 (19.5%)	79 (18.2%)
Other	11 (2.5%)	23 (5.3%)
Site of metastases		
Any site	422 (95.0%)	414 (95.4%)
Hilar nodes	164 (36.9%)	176 (40.6%)
Mediastinal nodes	228 (51.4%)	228 (52.5%)
Supraclavicular/scalene nodes	37 (8.3%)	34 (7.8%)
Ipsilateral lung	188 (42.3%)	177 (40.8%)
Contralateral lung	145 (32.7%)	147 (33.9%)
Pleura	111 (25.0%)	112 (25.8%)
Liver	74 (16.7%)	93 (21.4%)

Adrenal(s)	75 (16.9%)	54 (12.4%)
Bone	156 (35.1%)	126 (29.0%)
Bone marrow	2 (0.5%)	3 (0.7%)
Skin	9 (2.0%)	4 (0.9%)
Pleural effusion present		
n	444	433
Yes	169 (38.1%)	164 (37.9%)
No	275 (61.9%)	269 (62.1%)
Number of metastatic sites (baseline)		
n	444	433
< 4	320 (72.1%)	311 (71.8%)
≥ 4	124 (27.9%)	122 (28.2%)
Baseline tumor burden (cm) for patients with measurable disease		
n	394	386
Mean (SD)	8.5 (6.5)	9.0 (5.8)
Median	7	8
Range	1–80	1–30

NSCLC = non–small cell lung cancer; NOS = not otherwise specified;

The sponsor also summarized non-protocol therapy initiated prior to or after progression (see the following tables). Approximately 18% and 13% of patients in the CP and BV/CP arm received any antitumor therapy prior to progression. About 66% and 62% of patients in the CP and BV/CP arm received non-protocol antitumor therapy after progression. The most common treatment prior or after progression was chemotherapy Approximately 12% and 9% for CP and BV/CP arm, respectively, received chemotherapy prior to progression. Also about 50% and 48% for CP and BV/CP arm, respectively, received chemotherapy after progression.

Table 11 Sponsor's Non-Protocol Therapy Initiated Prior to Progression (Study E4599)

	CP (n=444)	BV/CP (n=434)
Number of randomized non-EPP patients	440	429
Any antitumor therapy prior to progression	81 (18.4%)	54 (12.6%)
Chemotherapy	54 (12.3%)	39 (9.1%)
Immunotherapy	5 (1.1%)	1 (0.2%)
Hormone therapy	1 (0.2%)	0 (0.0%)
Radiotherapy	21 (4.8%)	11 (2.6%)
Surgery	1 (0.2%)	3 (0.7%)
Other	9 (2.0%)	3 (0.7%)

Note: Non-protocol therapy prior to progression forms were not collected for EPP patients and EPP patients were not included in this table.

Table 12 Sponsor's Non-Protocol Therapy Initiated after Progression (Study E4599)

	CP (n=444)	BV/CP (n=434)
Number of randomized non-EPP patients	440	429
Any antitumor therapy after progression		
No	152 (34.5%)	164 (38.2%)
Yes	288 (65.5%)	265 (61.8%)
Type of therapy initiated		
Chemotherapy	220 (50.0%)	205 (47.8%)
Gemcitabine	73 (16.6%)	67 (15.6%)
Taxane	62 (14.1%)	77 (17.9%)
Other	112 (25.5%)	101 (23.5%)
Non-chemotherapy	108 (24.5%)	88 (20.5%)

Note: Non-protocol therapy prior to progression forms were not collected for EPP patients and EPP patients were not included in this table.

The medical and surgical history and concomitant therapy were not collected.

3.1.5.2 Primary Efficacy Endpoint Analyses

Based on the second interim efficacy analysis (March 9, 2005 with data cutoff of February 9, 2005), the DMC determined that the primary endpoint of overall survival had crossed the O'Brien-Fleming boundary in favor of the BV/CP arm and recommended that the results be release to the investigators for possible presentation and publication. This interim analysis included 72.2% of the total planned information of 650 deaths. However, a later dataset with better follow-up data had 581 deaths as of February 9, 2005. The results were summarizes in the following table:

Table 13 ECOG's Summary of Overall Survival – March 9, 2005 Second Interim Analysis based on Eligible Patient Population (Study E4599)

	CP (n=431)	BV/CP (n=424)
No. of patients who died	246 (57.1%)	223 (52.6%)
Duration of survival (months) [a]		
Median	10.2	12.5
95% CI	NA	NA
Stratified analysis [b]		
Hazard ratio (CP vs. BV/CP)	0.78	
95% Repeated Confidence Interval (RCI)	(0.62,0.98)	
p-value		
Wald test	0.0075	
Log-rank test (p-value)	0.0074	

CI = confidence interval; + = indicates a censored value.; NA=Not Available.

[a] Summaries of duration of survival (median, percentiles) were estimated from Kaplan-Meier curves. 95% CI for median was computed using the method of Brookmeyer and Crowley.

[b] Hazard ratios were estimated by Cox regression. The strata are tumor measurability (yes vs. no), prior radiotherapy (yes vs. no), weight loss (< 5% vs. ≥ 5%), and stage (IIIb vs. IV or recurrent).

Note : ECOG also performed analysis based on all randomized patient population. Based on 878 all randomized population, similar results were obtained (Wald test p-value=0.012, Repeated Confidence Interval=[0.64,0.99], logrank test p-value=0.012).

Based on the second interim results, the upper bound of the repeated confidence interval is less than 1 (0.98) , so the null hypothesis is rejected in favor of the BV/CP arm.

Reviewer's comment:

- *It is noted that the inference should be based on adjusted p-value after the 2nd interim analysis. The first interim analysis for OS was performed after 314 events (ECOG-eligible patient population) with a critical value of 3.02. The second interim analysis was statistically significant (p-value = 0.0120) based on 581 ITT events. Final p-value should be 0.0134. The 581 ITT events were obtained by this reviewer based on Feb. 9, 2005 cutoff date (i.e. for the 2nd interim analysis).*

  The 2nd interim analysis results performed by ECOG was based on 469 events (ECOG-eligible patient population) with a nominal p-value=0.0074. If the ECOG's 2nd interim analysis results were used, the final p-value would be 0.0086.

  It is recommended that a final p-value based on 581 deaths would be used for the inference since it provides more information for the study population at the 2nd interim analysis. Based on 581 deaths, the estimated treatment effects appears to be smaller than that based on 469 deaths. Hazard ratio estimates are 0.81 and 0.78 from data based on 581 deaths and 469 deaths, respectively.

- *It is noted that Repeated Confidence Interval approach may not be desirable since the parameter of interest based on this procedure is not fixed. However, Genentech shows that the log-rank test (p-value=0.0074) also crossed the O'Brien-Fleming boundary (critical value = 2.413) which confirms the result based on Repeated Confidence Interval approach.*
  It is also noted that the sponsor's presented 95% repeated confidence interval is not a 95% confidence interval, it is, instead, a 98.3% RCI. The 95% RCI at the

time of the second interim analysis is roughly (0.65, 0.94).

- *It is also noted that all efficacy analyses should be based on ITT population, however ECOG performed the interim analyses based on eligible patient population. Based on ECOG's log rank test using the ITT population, the result (nominal p-value=0.012) appears to support the sponsor's conclusion. .*

The final analysis of the overall survival was performed based on the most current and complete efficacy data (received from ECOG on December 30, 2005). In the final analysis, the BV/CP arm again show beneficial treatment effect on overall survival based on the stratified log rank test (p-value=0.0030). The median survival time was 10.2 months for CP arm and 12.5 months for BV/CP arm.

Table 14 Sponsor's Summary of Overall Survival – Final Analysis (Study E4599)

	CP (n=444)	BV/CP (n=434)
No. of patients who died	363 (81.8%)	335 (77.2%)
No. of patients alive	81 (18.2%)	99 (22.8%)
Duration of survival (months) [a]		
Median	10.3	12.3
95% CI	(9.36, 11.73)	(11.30, 13.73)
25th–75th Percentile	5.7–18.8	7.0–22.3
Minimum–maximum	0.0+–49.0	0.0+–48.2+
Stratified analysis [b]		
Hazard ratio (relative to CP)	0.80	
95% CI	(0.69, 0.93)	
p-value (relative to CP)		
Log-rank	0.0030	

CI = confidence interval; + = indicates a censored value.

[a] Summaries of duration of survival (median, percentiles) were estimated from Kaplan-Meier curves. 95% CI for median was computed using the method of Brookmeyer and Crowley.

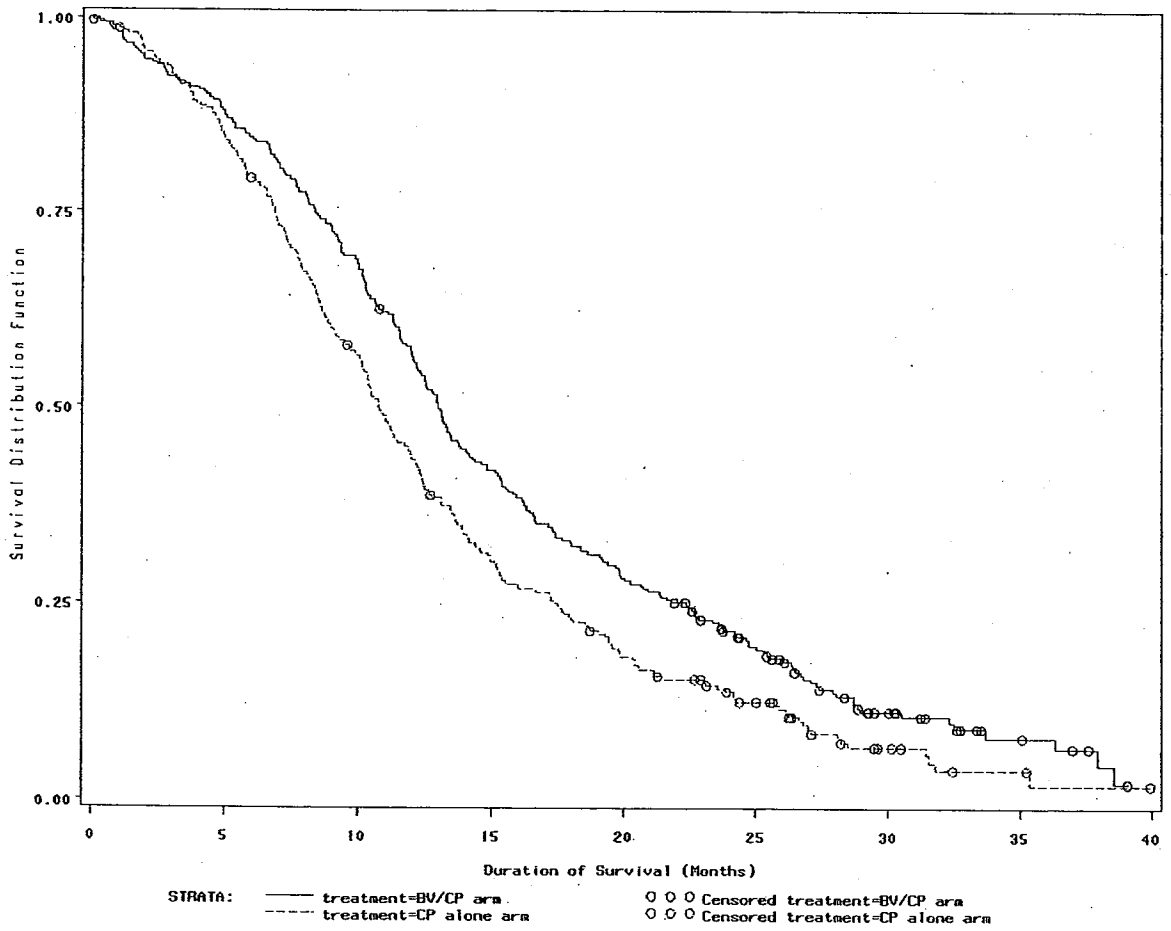
[b] Hazard ratios were estimated by Cox regression stratified by the stratification factors indicated earlier.

Reviewer's comment:

- The estimated mean survival times and the standard errors are 12.96 (se=0.5123) and 15.67 (se=0.6018) for CP and BV/CP arm, respectively.

The Kaplan-Meier plot of the overall survival results based on the submitted data is shown in the following figure:

Figure 1 Kaplan-Meier estimates for Overall Survival



Reviewer's Comments:

- *This reviewer performed stratified log rank test to evaluate treatment difference based on the overall survival data with the censoring and event indicator switched. The median censoring time were 24.2 months and 24.7 months for CP and BV/CP arm, respectively.*
- *Genentech performed sensitivity analysis by assuming patients who were lost to follow-up in the BV/CP arm to have died, while patients in the CP arm were censored at the date of last contact. It is noted that patients who were alive at the database transfer date but whose last contact date was more than 180 days before the date of the final database cutoff (December 30, 2005) were considered as lost to follow-up in this sensitivity analysis. There were 9.0% (40/444; 81 patients who were still alive) and 7.8% (34/434; 99 patients who were still alive) of the patients in the CP and BV/CP arm, respectively, had lost-to-follow-up for 180 days or more before the date of the final database cutoff. The results show that the survival advantage in the BV/CP arm does not hold with a nominal p-value of 0.0628 based on stratified log-rank test.*

Table 15 Sponsor's Sensitivity Analysis of Overall Survival (Study E4599)

	CP (n=444)	BV/CP (n=434)
No. of patients who died	363 (81.8%)	369 (85.0%)
No. of patients alive	81 (18.2%)	65 (15.0%)
Duration of survival (months) [a]		
Median	10.3	12.0
95% CI	(9.36, 11.73)	(11.04, 13.08)
Stratified analysis		
Hazard ratio (relative to CP) [b]	0.870	
95% CI	(0.751, 1.008)	
p-value (relative to CP)		
Log-rank	0.0628	

CI = confidence interval;

+ indicates a censored value.

[a] Summaries of duration of survival (median, percentiles) were estimated from Kaplan-Meier curves. 95% CI for median was computed using the method of Brookmeyer and Crowley.

[b] Hazard ratios were estimated by Cox regression stratified by the stratification factors indicated earlier.

- *Genentech also performed Cox's proportional hazards model to evaluate treatment effect (BV/CP v.s. CP alone arm) after adjusting for important prognostic factors (see subgroup analysis in section 16.1.9 Documentation of Statistical Methods of the clinical report). Several important prognostic factors for overall survival were identified : weight loss (<5%, ≥ 5%), ECOG performance status at study entry (0,≥1), gender (male, female), baseline SLD(sum of longest diameters of target lesions; treated as continuous variable) and stage (stage IV vs IIIb; recurrent vs. stage IIIb). These baseline prognostic factors show nominally significant effect on overall survival based on the Cox's model that each of these factors entered the model individually along with treatment. After adjusting for these prognostic factors, the treatment effect remains statistically significant in favor of the CP +bevacizumab arm.*

3.1.5.3 Secondary Efficacy Endpoint Analyses

The progression-free survival (PFS) is summarized in the following table. The results showed that BV/CP arm had longer median progression-free survival (6.4 months) as compared with that of the CP alone arm (4.8 months) with p value of <0.0001 from the stratified log rank test. Approximately 72-78% of the PFS events were attributed to disease progression and the rest of the events were attributed to deaths.

Table 16 Sponsor's Summary of Progression-Free Survival (Study E4599)

	CP (n=444)	BV/CP (n=434)
No. patients with an event	348 (78.4%)	341 (78.6%)
Earliest contributing event		
Disease Progression	273 (78.45%)	247 (72.43%)
Death	75 (21.55%)	94 (27.57%)
No. of patients without an event	96 (21.6%)	93 (21.4%)
PFS (months) [a]		
Median	4.8	6.4
(95% CI)	(4.40, 5.39)	(6.11, 6.87)
25th 75th Percentile	2.3–7.3	3.7–10.5
Minimum–maximum	0.0+–35.0	0.0+–41.7
Stratified analysis [b]		
Hazard ratio (relative to CP)	0.654	
(95% CI)	(0.561, 0.764)	
p-value (relative to CP)		
Log-rank	<0.0001	

+ indicates a censored value: CI=confidence interval.

[a] Summaries of duration of survival (median, percentiles) were estimated from Kaplan-Meier curves. 95% CI for median was computed using the method of Brookmeyer and Crowley.

[b] Hazard ratios were estimated by Cox regression stratified by the factors used in stratified randomization.

Reviewer's Comments:

- *This reviewer performed stratified log rank test to evaluate treatment difference based on the sponsor calculated progression free survival data with the censoring and event indicator switched. The results show that the a marginally*

longer time to censoring in the BV/CP arm (nominal p-value=0.05 based on stratified log rank test; the median time to censoring were 23 months [95% C.I.=17.1, 24.3] and 22 months [95% C.I.=18.0, ∞] for CP+bevacizuma and CP arm, respectively).

It is noted that the censoring scheme that censored patients who took non-protocol therapy at the last tumor assessment prior to the non-protocol therapy (about 18% and 13% of CP and CP/BV patients, respectively) may contribute to the differential duration of time to censoring. When this reviewer switched the censoring indicator for one of the sensitivity analysis (i.e. ignore the non-protocol therapy status, see the analysis results followed this reviewer's comments) and performed similar analysis based on stratified log-rank test,, the results did not suggest a differential censoring distribution (nominal p-value=0.68).

This reviewer performed three sensitivity analyses. The first sensitivity analysis censored patients who did not progress or die at the date of the last tumor assessment regardless whether the patients took non-protocol specified anti-tumor therapy or not. The second sensitivity analysis is based on the "worst case" scenario in which patients who did not progress or die, but had taken non-protocol anti-tumor therapy were censored at the date of the last tumor assessment prior to non-protocol specified anti-tumor therapy for the CP arm, while the same group of patients for BV/CP arm were treated as event occurred at the time of non-protocol specified anti-tumor therapy. The last sensitivity analysis is to treat all patients who did not progress or die, but had taken non-protocol anti-tumor therapy to be events at the time of the last tumor assessment prior to non-protocol specified anti-tumor therapy. All three analyses confirmed significantly longer time to progression in the BV/CP arm (nominal p-value ≤ 0.001 for both analyses).

Table 17 Reviewer's Sensitivity Analyses of Progression-Free Survival (Study E4599)

	CP (n=444)		BV/CP (n=434)
PFS (months)Sensitivity Analysis 1 [a]			
No. patients with an event	415 (93.5%)		386 (88.9%)
Median	4.8		6.4
(95% CI)	(4.4, 5.4)		(6.1, 6.9)
Hazard ratio (relative to CP)		0.69	
(95% CI)		(0.60, 0.80)	
p-value (log rank)		<0.0001	
PFS Sensitivity Analysis 2 [b]			
No. patients with an event	348 (78.4%)		394 (90.8%)
Median	4.8		5.9
(95% CI)	(4.4, 5.4)		(5.4, 6.3)
Hazard ratio (relative to CP)		0.78	
(95% CI)		(0.67, 0.90)	
p-value (log rank)		0.001	
PFS Sensitivity Analysis 3 [c]			
No. patients with an event	424 (95.5%)		394 (90.8%)
Median	4.1		5.9
(95% CI)	(3.6,4.3)		(5.4, 6.3)
Hazard ratio (relative to CP)		0.64	
(95% CI)		(0.56,0.74)	
p-value (log rank)		<0.0001	

[a] Ignore non-protocol –specified anti-tumor therapy, i.e. patients who took non-protocol-specified anti tumor therapy and who did not have PFS event were censored at the date of the last tumor assessment.

[b] Worst case analysis : Patients in the CP group who took non-protocol –specified anti-tumor therapy were censored; patients in the CP/BV group who took non-protocol –specified therapy were treated as having PFS events at the time of taking the non-protocol-specified anti-tumor therapy.

[c] Set all NPT as event analysis : this is to treat all patients who did not progress or die, but had taken non-

protocol specified anti-cancer therapy to be events at the time of the last tumor assessment prior to non-protocol anti-cancer therapy.

Reviewer's Comments:

- *While the reviewer confirms the Genentech's finding on PFS based on the submitted data, a cautionary interpretation of the data is recommended based on the following findings:*

  a. *The sponsor indicated that the frequencies of tumor assessment are different between treatment arms after end of chemotherapy. The tumor assessment will be performed every 12 weeks for the CP arm after the end of the protocol specified therapy and every 9 weeks for the BV/CP arm after the end of chemotherapy and during the continuous bevacizumab treatment until disease progression or death. The differential tumor assessment schedules between arms may result in ascertainment bias in PFS. If the sponsor's stated tumor assessment is followed through, it is noted that the differential assessment schedule may penalize the BV/CP arm more than the CP arm since the BV/CP arm had a more frequent schedule which may have higher chance to find abnormality. However, based on this reviewer's observation, the sponsor's stated schedules of tumor evaluation was not strictly followed and there were more unscheduled visits occurred for the CP alone arm compared with those of the BV/CP arm. The magnitude and direction of the bias introduced by the differential timing of tumor assessment can not be determined based on the data submitted.*

  b. *Since the imaging data was not collected based on standard operating procedure and the overall response seems to be derived from investigator assessment, the validity of the progression free survival results can not be confirmed.*

The following table shows the objective response summarized by Genentech based on patients with measurable disease. The BV/CP arm appears to have higher objective response rate as compared with the CP alone arm (29.0% and 12.9% for BV/CP and CP alone arm, respectively; p-value<0.0001 based on Cochran-Mantel-Haenszel test). The sponsor also performed sensitivity analysis based on all randomized patients. Similarly,

the objective response rate is higher in the BV/CP arm compared with CP arm (26.7% vs. 11.9%, p-value<0.0001).

Table 18 Sponsor's Summary of Objective Response for patients with Measurable Disease (Study E4599)

	CP (n=403)	BV/CP (n=397)
No. patients with objective response (%)	52 (12.9%)	115 (29.0%)
Best objective response		
Complete response [a]	2 (0.5%)	5 (1.3%)
Partial response	50 (12.4%)	110 (27.7%)
95% CI for objective response [b]	(9.9%, 16.7%)	(24.6%, 33.7%)
Difference in objective response rates (%)		
BV/CP – CP	16.1%	
(95% CI) [c]	(10.5%, 21.6%)	
p-value [c]	<0.0001	

[a] Complete response as best objective response required a CR confirmed by a CR; otherwise, the best objective response was a partial response.

[b] Computed using the Fleiss approximation to the normal CIs.

[c] 95% C.I. was computed using the standard normal approximation. P-value is from Stratified Cochran-Mantel-Haenszel Chi-Squared Test.

Reviewer's comment:

- *Similar comments for the PFS can be applied here. Due to the different tumor assessment schedule between arms after chemotherapy, the impact on the objective response can not be assessed. Also, the validity of the response results can not be confirmed since the imaging data was not collected based on standard operating procedure and the overall response seems to be derived from investigator assessment.*

The following table shows the duration of objective response summarized by Genentech. The median duration of response based on the responders was longer in the BV/CP arm than that in the CP arm (6.2 months versus 5.0 months) . Since the

imaging data was not adequately collected, further evaluation of the objective response and duration of objective response was not performed.

Table 19 Sponsor's Summary of Duration of Objective Response for patients with Measurable Disease (Study E4599)

	CP (n=403)	BV/CP (n=397)
No. of patients with an objective response	52	114
No. of patients with an event	38 (73.1%)	90 (78.9%)
No. of patients without an event	14 (26.9%)	24 (21.1%)
Duration of objective response [a]		
Median (Months)	5.0	6.2
95% CI	(4.30, 5.85)	(5.55, 7.13)
25th–75th percentile	4.0–6.9	4.6–9.5
Minimum–maximum	1.0+–21.1+	1.3+–32.1+
Stratified analysis [b]		
Log-rank p-value	0.0278	

Reviewer's comments :

- *In the SAP, the sponsor indicates that the formal hypothesis testing will not be performed and the analysis is for descriptive purpose because this analysis of duration of objective response is based on a non-randomized subset of patients.*

3.1.5.4 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Genentech concluded that the addition of bevacizumab to Paclitaxel+Carboplatin chemotherapy regimen, followed by bevacizumab alone, in patients previously untreated for locally advanced or metastatic NSCLC other than squamous-cell carcinoma resulted in clinical meaningful and statistically significant prolongation of survival. The survival benefit in the BV/CP arm was seen in the pre-specified patient subgroups defined by measurable disease, prior radiation therapy, ECOG performance status at study entry, race and tumor burden. However, Genentech indicated that improvement in overall

survival was not seen in females, patients aged 65 years or older, weight loss of 5% or greater in the 6 months prior to enrollment, or histologic subtypes other than adenocarcinoma. Genentech explained that this survival results were inconsistent with the benefit of bevacizumab treatment demonstrated based on objective response and PFS. Also the small size of the subgroup populations in some cases may have limited power to show treatment effect.

In addition, Genentech concluded that the BV/CP arm had clinically meaningful and statistically significant improvements in objective response rate and PFS.

This reviewer's confirmed Genentech's overall survival results that show a beneficial treatment effect in favor of BV/CP arm : the median survival times were 12.3 months and 10.3 months for BV/CP arm and CP alone arm, respectively. The beneficial treatment effect based on overall survival was consistent across various subgroups, except in females, patients aged 65 years or older, histologic subtypes other than adenocarcinoma and patients with baseline weight loss ≥5 (see the Section 4: Finding in Special/Subgroup Populations).

This reviewer also confirmed Genentech's objective response and PFS, that show a favorable result of BV/CP arm as compared with CP arm. However, a cautionary interpretation of the results on objective response and progression free survival is recommended due to the concern that the validity of the data can not be confirmed and the impact of differential tumor assessment schedules between arms on study results is not clear.

4 Findings in Special/Subgroup Populations

This section provides summary statistics (hazard ratio, median survival time, count of patients) based on selected subgroups for overall survival.

4.1 Gender

Sub-group analyses based on gender for overall survival were performed by this reviewer. The BV/CP arm shows nominally significant lower risk as compared with the

CP alone arm in the male subgroup. However, BV/CP arm did not show beneficial effect in female subgroup.

Table 20 Reviewer's Summary of Overall Survival in the Primary Arms by Gender (Study E4599)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio	CP (n=444)		BV/CP (n=434)	
					# of patients	Median survival time (95%C.I.)	# of patients	Median survival time (95%C.I.)
Overall Survival	Female	400	0.9490	0.99(0.79,1.25)	185	13.2(11.2,14.4)	215	13.3(11.7,16.6)
	Male	478	<0.001	0.69(0.57,0.85)	259	8.9(7.8,10.2)	219	11.7(9.9,13.2)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

Reviewer's comment:

- *When the sponsor fitted a Cox's model including treatment, each prognostic factor (gender, age and weight loss), and treatment by the individual prognostic factor interaction, the result shows a nominally significant treatment by gender interaction.*

- *Since the data suggests differential treatment effect based on gender subgroup, this reviewer performed a few analyses and tried to find out if any factor that might contribute such discrepancy. By investigating a few baseline characteristics, the result did not show any notable imbalance (see appendix). It is not clear if there is anyclinical explanation that may lead to the gender difference.*

4.2 Race

Sub-group analyses based on race subgroup for overall survival were performed by this reviewer. The BV/CP arm consistently showed lower risk than the CP alone arm (Demonstrated by lower than one hazard ratio) across race subgroups.

Table 21 Reviewer's Summary of Overall Survival by Race (Study E4599)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio	CP (n=444)		BV/CP (n=434)	
					# of patients	Median survival time (95%C.I.)	# of patients	Median survival time (95%C.I.)
Overall Survival	Non-white	125	0.0440	0.66(0.44,0.99)	57	10.7(7.1,13.2)	68	15.5(12.4,17.9)
	White	753	0.0230	0.83(0.71,0.98)	387	10.3(9.2,11.8)	366	11.9(10.7,13.2)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model

4.3 Age

Sub-group analyses based on age subgroup (<65; ≥ 65 years old) for overall survival were performed by this reviewer. The BV/CP arm showed lower risk in overall survival as compared with the CP alone arm in patients younger than 65 years old. However, the lower risk trend is less clear in patients of 65 years or older.

Table 22 Reviewer's Summary of Overall Survival by Age Subgroup (Study E4599)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio	CP (n=444)		BV/CP (n=434)	
					# of patients	Median survival time (95%C.I.)	# of patients	Median survival time (95%C.I.)
Overall Survival	<65	499	0.0010	0.72(0.59,0.88)	250	9.8(8.6,11.1)	249	13.1(11.8,15.4)
	≥ 65	379	0.3990	0.91(0.72,1.14)	194	11.7(9.1,13.7)	185	11.3(9.6,13.2)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

4.4 Other Special/Subgroup Populations

Additional subgroup analyses based on several baseline prognostic factors were performed by this reviewer. BV/CP arm had consistently lower risk (indicated by less than 1 or close to 1 hazard ratio) in overall survival, except the histologic subtype other than adenocarcinoma and patients with baseline weight loss ≥5% where the trend is less clear.

Table 23 Reviewer's Summary of Overall Survival by Baseline Prognostic Factors (Study E4599)

Endpoint	Level	# of Patients	P-value[a]	Hazard Ratio (95% C.I.)	CP (n=444)		BV/CP (n=434)	
					# of patients	Median survival time (95%C.I.)	# of patients	Median survival time (95%C.I.)
ECOG PS status	0	346	0.09000	0.81(0.63,1.03)	175	13.3(10.8,15.8)	171	15.6(13.3,17.5)
	>=1	528	0.01300	0.79(0.65,0.95)	268	9.4(7.8,10.2)	260	10.8(9.7,12.3)
	Unknown	4	--	--	--	--	--	--
Baseline sum of longest diameters	< 3 cm	117	0.47800	0.85(0.55,1.32)	63	12.0(9.1,15.8)	54	15.6(10.9,22.3)
	≥ 3 cm	665	0.03200	0.83(0.70,0.98)	332	9.8(8.7,11.6)	333	11.8(10.7,13.1)
	Unknown	96	--	--	--	--	--	--
Disease measurability	No	77	0.03000	0.54(0.31,0.94)	41	9.7(7.3,16.7)	36	15.6(10.8,33.1)
	Yes	800	0.01700	0.83(0.71,0.97)	403	10.3(9.2,11.8)	397	12.1(11.0,13.3)
	unknown	1	--	--	--	--	--	--
Histology	Adenocarcinoma	602	0.00000	0.69(0.58,0.83)	302	10.3(9.1,11.7)	300	14.2(12.4,16.1)

	Bronchoalveolar	23	0.42300	1.48(0.57,3.89)	11	17.7(6.2,21.1)	12	10.0(5.7,15.2)
	Large Cell Undinsclc, NOS	48	0.67000	1.15(0.60,2.24)	30	8.7(7.6,17.3)	18	10.0(6.6,17.0)
	NSCLC, NOS	165	0.37300	1.16(0.84,1.61)	86	10.0(8.0,13.0)	79	9.5(7.0,11.5)
	Other	34	0.83100	0.92(0.43,1.98)	11	12.6(5.4,19.1)	23	8.4(6.4,16.7)
	Squamous	3	0.99900	0.00(0.00,-)	2	12.3(0, ∞)	1	22.4(0, ∞)
	Unknown	3	--	--	--	--	--	--
Prior radio therapy	No	795	0.00800	0.81(0.69,0.95)	403	10.3(9.4,11.8)	392	12.2(11.1,13.3)
	Yes	80	0.14100	0.70(0.43,1.13)	41	10.7(7.9,12.9)	39	14.1(9.3,17.6)
	Unknown	3	--	--	--	--	--	--
Stage	IIIB (not recurrent)	108	0.09500	0.68(0.43,1.07)	56	11.0(9.1,12.7)	52	15.5(11.0,19.6)
	IV (Not recurrent)	669	0.10800	0.87(0.74,1.03)	345	9.5(8.5,10.8)	324	11.1(10.1,12.3)
	Recurrent	99	0.05800	0.61(0.37,1.02)	42	17.7(14.1,19.8)	57	21.8(16.8,-)
	Unknown	2	--	--	--	--	--	--
Baseline weight loss ≥5%	No	624	0.00000	0.72(0.60,0.87)	316	12.0(10.6,13.2)	308	14.1(12.4,15.6)
	Yes	247	0.77000	0.96(0.73,1.26)	127	7.4(6.2,9.4)	120	8.4(7.2,10.8)
	Unknown	7	--	--	--	--	--	--

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

Reviewer's comment:

- *The BV/CP vs. CP overall survival hazard ratio varied across subgroups of histology type and baseline weight loss. . The interpretation should be taken with caution since the numbers of events for the subgroups are small.*

5 Summary and Conclusions

Genentech submitted study E4599, a Phase II/III randomized, multi-center, open-label, randomized, active-controlled clinical study, to support bevacizumab in combination with carboplatin/paclitaxel chemotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) of non-squamous histology.

In study E4599, patients were randomized to paclitaxel+carboplatin chemotherapy arm or paclitaxel+carboplatin combined with bevacizumab arm. The randomization was stratified by tumor measurability (yes, not), prior radiotherapy (yes, no), weight loss (<5%, ≥5%) and stage (IIIV, IV or recurrent). Bevacizumab was administered at a dose of 15 mg/kg every three weeks for patients in the BV/CP. The bevacizumab dose was administered immediately following carboplatin on day 1 of each cycle until relapse or disease progression. Patients in the BV/CP arm could continue on bevacizumab treatment after early discontinuation of paclitaxel/carboplatin.

A total of 878 patients were randomized to each arm : 444 or 434 for CP and BV/CP arm, respectively.

In study E4599, the primary efficacy endpoint was overall survival. The objective response rate and progression free survival were designated as the important secondary efficacy endpoints.

A summary of the primary efficacy endpoint of study E4599 (using the submitted data) is presented in the following table based on stratified log-rank test for the p-value, Cox's proportional hazards model for the hazard ratios and Kaplan Meier method for calculating the median survival times for each treatment arm.

Table 24 Summary of Primary and Key Secondary Efficacy Endpoint – (Study E4599)

Endpoint	Characteristics	CP (n=444)	BV/CP (n=434)
Overall Survival	# of Death	363	335
	Duration of survival[a] (mon.)		
	Median	10.3	12.3
	(95% CI)	(9.36, 11.73)	(11.30, 13.73)
	Range	0.0+–49.0	0.0+–48.2 +
	Stratified analysis (relative to CP)		
	Hazard ratio [b]	0.80	
	(95% CI)	(0.69, 0.93)	
	Nominal p-value (log rank)	0.0030	
	Final p-value [c]	0.0134	

CI = confidence interval; NA = not applicable; + indicates a censored value.

[a] Summary statistics are from Kaplan-Meier survival estimates; 95% CI was computed using the method of Brookmeyer and Crowley.

[b] Estimated by Cox's model stratified by tumor measurability (yes,no), prior radiotherapy (yes, no), weight loss (<5%, ≥5%) and stage (IIIv, IV or recurrent).

[c] The first interim analysis for OS was performed after 314 events (ECOG-eligible patient population) with a critical value of 3.02. The second interim analysis was statistically significant (p-value = 0.0120) and performed after 581 ITT events. Based on these interim analysis results, the final p-value is obtained.

5.1 Statistical Issues and Collective Evidence

The results show beneficial treatment effect in favor of BV/CP arm. The median survival times were 12.3 months and 10.3 months for BV/CP arm and CP alone arm, respectively. The beneficial treatment effect of the BV/CP arm is consistently demonstrated in various subgroups defined by measurable disease, prior radiation therapy, ECOG performance status at study entry, race and tumor burden. There was a lack of internal consistency in an estimated effect for gender, age and weight change

subgroups. The beneficial treatment effect was not clear in female (hazard ratio=0.99, 95% C.I.=[0.79, 1.25]), patients aged 65 years or older (hazard ratio=0.91, 95% C.I.=[0.72, 1.14]), patients with baseline weight loss of 5% or greater in the 6 months prior to enrollment (hazard ratio=0.96, 95% C.I.=[0.73, 1.26]) or histologic subtypes other than adenocarcinoma (although many categories had small cell sizes).

The sponsor also has shown a treatment effect in favor of BV/CP arm based on objective response rate and PFS. However, due to the concern of the validity of the data that can not be confirmed and the impact of differential tumor assessment schedules that is not clear, a cautionary interpretation of the objective response and PFS results is recommended.

The major statistical/data issues were summarized as follows:

- The sponsor shows significant survival benefit in the BV/CP arm as compared with CP arm alone. However, several issues were noted for the overall survival results:
  a. Only one trial was submitted to support the NSCLC indication.
  b. Lack of internal consistency of the results.
- It is noted that the planned frequency of tumor assessment post chemotherapy is not consistent between treatment arms. The differential tumor assessment schedules between arms may result in ascertainment bias in PFS. Based on this reviewer's observation, the sponsor's stated schedules of tumor evaluation was not strictly followed and there were more unscheduled visits occurred for the CP alone arm compared with those of the BV/CP arm. The magnitude and direction of the bias introduced by the differential timing of tumor assessment can not be determined based on the data submitted.
- In the sponsor's analysis of PFS, patients who took non-protocol specified anti-tumor therapy were censored at the last tumor assessment prior to the non-protocol specified anti-tumor therapy. It is noted that this censoring scheme may be informative censoring and lead to estimates that do not unbiasedly estimate the parameters of the PFS.
- Due to different adverse event reporting requirement and different source of data collection, the adverse event results can not be confirmed.

- Several data collection/database quality issues were identified. For example, the stratification factor data collected based on ECOG eligibility form are not consistent with the data collected from the CRF pages.

5.2 Conclusions and Recommendations

Based on study E4599, the results demonstrate beneficial treatment effect of BV/CP arm on overall survival as compared with CP alone arm (the median survival times were 12.3 months and 10.3 months for BV/CP arm and CP alone arm, respectively). The trend of beneficial treatment effect in BV/CP arm on overall survival was mostly consistent across various subgroups defined by measurable disease, prior radiation therapy, ECOG performance status at study entry, race and tumor burden. It is not clear that there is an effect in female, patients aged 65 years or older, patients with baseline weight loss of 5% or greater in the 6 months prior to enrollment or histologic subtypes other than adenocarcinoma.

Since imaging data was not collected based on standard procedure and different tumor assessment schedules between arms, the results of progression free survival or objective response should be interpreted with caution.

6 Appendix

6.1 Summary of Distribution of Potential Prognostic factors by gender group

A summary of the distribution of potential prognostic factors by gender group was performed by this reviewer. The purpose of this summary is to evaluate whether there is noticeable imbalanced between gender groups and the finding may be used to explain the gender difference in the treatment effect. Based on this summary, there is no noticeable difference in the distribution between gender groups.

Table 25 Reviewer's Summary of the Distribution of Potential Prognostic Factors Across the Two Treatment Groups and Region (Study E4599)

Factor	Number (%) of patients			
	Female		Male	
	CP N=185	BV/CP N=215	CP N=259	BV/CP N=219
Baseline weight loss ≥ 5%				
No	136 (73.91%)	144 (67.92%)	180 (69.50%)	164 (75.93%)
Yes	48 (26.09%)	68 (32.08%)	79 (30.50%)	52 (24.07%)
Stage				
IIIB (not recurrent)	25 (13.51%)	23 (10.75%)	31 (12.02%)	29 (13.24%)
IV (not recurrent)	140 (75.68%)	156 (72.90%)	205 (79.46%)	168 (76.71%)
Recurrent	20 (10.81%)	35 (16.36%)	22 (8.53%)	22 (10.05%)
Measurable disease				
No	165 (89.19%)	193 (89.77%)	233 (89.96%)	198 (90.41%)
Yes	20 (10.81%)	22 (10.23%)	26 (10.04%)	21 (9.59%)
Prior radiotherapy				
No	170 (91.89%)	195 (91.98%)	233 (89.96%)	197 (89.95%)
Yes	15 (8.11%)	17 (8.02%)	26 (10.04%)	22 (10.05%)
ECOG performance status				
0	72 (39.13%)	86 (40.38%)	103 (39.77%)	85 (38.99%)
1	112 (60.87%)	127 (59.62%)	156 (60.23%)	133 (61.01%)
Age				
40-64	109 (58.92%)	125 (58.14%)	137 (52.90%)	115 (52.51%)
<40	1 (0.54%)	5 (2.33%)	3 (1.16%)	4 (1.83%)
≥65	75 (40.54%)	85 (39.53%)	119 (45.95%)	100 (45.66%)
Race				
Non-white	21 (11.35%)	38 (17.67%)	36 (13.90%)	30 (13.70%)
White	164 (88.65%)	177 (82.33%)	223 (86.10%)	189 (86.30%)
Baseline sum of longest diameter of tumor				
≤ 3 cm	29 (17.90%)	22 (11.52%)	34 (14.59%)	32 (16.33%)
> 3cm	133 (82.10%)	169 (88.48%)	199 (85.41%)	164 (83.67%)

Histology				
Adenocarcinoma	127 (68.65%)	152 (71.03%)	175 (68.09%)	148 (67.58%)
Bronchoalveolar	5 (2.70%)	5 (2.34%)	6 (2.33%)	7 (3.20%)
Large Cell Undifferentiated	13 (7.03%)	5 (2.34%)	17 (6.61%)	13 (5.94%)
NSCLC, NOS[a]	34 (18.38%)	42 (19.63%)	52 (20.23%)	37 (16.89%)
Other	6 (3.24%)	9 (4.21%)	5 (1.95%)	14 (6.39%)
Squamous	- (-%)	1 (0.47%)	2 (0.78%)	- (-%)

[a] NOS : Not otherwise specified.

6.2 Summary of Results from the Data Monitoring Committee Meeting

Based on ECOG's report for the second interim analysis and Genentech's summary, here is a summary of the meeting decision for the semi-annual meetings other than the two interim analyses:

Per protocol, the first suspension occurred after 111 patients enrolled (suspended from **February 22, 2002 to August 8, 2002**) to allow toxicity data on the first two cycles of therapy to be submitted to the statistical center. On **April 3, 2002** meeting, The DMC agrees that 100 patients who had received at least 2 cycles of therapy or had terminated the study prematurely will be reviewed.

On **June 28, 2002**, the DMC reviewed a summary of toxicity on the first 111 patients (103 had toxicity information in the database as of **June 21, 2002**) . Based on these results, the DMC recommended re-opened the study (**August 8, 2002**). At this time, the protocol specified criteria for early stopping based on excessive toxicity were not met. Due to the observation of one of the first bleeding related deaths on the bevacizumab arm was a patient with a prior history of hemoptysis, the DMC recommended that this study be reopened to accrual pending protocol to be amended to exclude patients with prior gross hemoptysis..

On October 30, 2002, the DMC reviewed the adverse events and recommend the study continued as planned.

Based on original design, it included another suspension of accrual after 336 eligible patients had been enrolled for allowing additional follow-up on toxicity and for the first interim analysis of survival to be performed. As of **May 30, 2003**, 5 patients (out of a total of 337) from BV/CP arm had had grade 4 or 5 hemorrhagic events, with none on CP (1-sided p-value of 0.03 based on Fisher's exact test). Note: as of **March 9, 2004** (second interim analysis), there were 13 hemorrhagic events occurred on the BV/CP arm and the difference between treatment arms was statistically significant (1-sided p-value=0.0001). By the time of the meeting, there have been two bleeding related deaths reported on the CP arm. The ECOG report said that these events were not included in the monitoring analysis of bleeding events because they were not reported as such through the expedited reports.

On **April 22, 2003**, since the data was approaching the planned suspension point, the DMC therefore reviewed the adverse event data and early survival and PFS to consider whether the planned suspension of accrual was necessary. At this time, with only 91 PFS events, the PFS data were already showing a substantial difference (estimated median PFS of 4.6 vs. 6.5 months) and the survival hazard ratio (based on 63 deaths) was larger than 1.1 (CP vs BV/CP) required for continuation of the study at the first interim analysis. Since the toxicity data looks reasonable, the DMC recommended that the design be modified to drop the planned suspension (amendment 4, **August 28, 2003**) and that this study should remain open to accrual during this period.

On **November 5, 2003**, the DMC again reviewed toxicity data. At this meeting, the study chair and the ECOG Thoracic Committee requested that the DMC consider modifying the design to provide adequate power for a smaller difference in survival. Although the rate of bleeding events continued to be concerned, the DMC did not believe changes to the protocol were required at this time and recommended approval of a proposal to increase the sample size to approximately 900 patients. The revised design was implemented in protocol addendum 6 (**January 29, 2004**).

At the November, 2003 DMC meeting, the DMC recommend further changes of study design to provide adequate power for a smaller treatment difference. Specifically, the DMC recommended dropping the requirement for a minimum observed 10% improvement in survival at 218 deaths and increasing the total number of patients to

provide at least 90% power for a 30% improvement in survival and 80% power for a 25% improvement. The reason for dropping the requirement for an observed improvement of at least 10% at the early analysis was because this stopping rule reduces the power of the study, but with the rapid accrual, this analysis in unlikely to be performed early enough to reduce the number of patients entered, and so will not serve a useful purpose.

7 SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer: **Date:** September 25, 2006

Dr. Yuan-Li Shen
Mathematical Statistician Yuan-Li Shen 9/25/06

Concurrence:

Mark Rothmann 9/25/06

Dr. Mark Rothmann
Statistical Team Leader

Aloka Chakravarty
9/25/06
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Director

CC:

HFD-107/ Gootenberg, Keegan, Sickafuse, Summers
HFD-711/Chakravarty, Rothmann, Shen
HFD-700/O'Neill, Patrician

This review consists of 55 pages (53 pages of text)
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125085/85

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

10-5-06

STN: 125085/85	Submission Date(s): 4/10/06, 5/1/06, 6/26/06
Brand Name	AVASTIN®
Generic Name	Bevacizumab
Reviewer	Hong Zhao
Supervisor	Nam Atiqur Rahman
OCP Division	DCP 5/OCP
Clinical Division	Biologic Oncology Products
Sponsor	Genentech
Relevant IND(s)	BB-IND 7023, 7921 (NCI), BLA 125085/0
Submission Type; Code	Efficacy Supplement, Priority Review
Formulation; Strength(s)	Single-use vials containing a 100 mg/4 mL or 400 mg/16 mL phosphate-buffered solution to be diluted in 0.9% saline for 60-90 minutes of intravenous infusion
Proposed Indication	Avastin, in combination with carboplatin and paclitaxel is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non– squamous, non-small cell lung cancer

1 Executive Summary

1.1 Recommendation

The results of clinical pharmacology and pharmacokinetic studies support the approval of the proposed indication. The sponsor is requested to accept the FDA recommended labeling statement describing the results of pharmacokinetic drug-drug interaction between bevacizumab and paclitaxel/carboplatin.

1.2 Phase IV Commitments

There are no Phase IV commitments requested from Clinical Pharmacology and Biopharmaceutics perspective. The following clinical Phase IV commitments are requested:

1. To submit either an efficacy supplement or the final study report for the Hoffman-LaRoche-sponsored study, BO17704. An efficacy supplement containing revised labeling should be submitted if the study results do not demonstrate a survival

benefit in females on the cisplatin and gemcitabine plus Bevacizumab arm compared to the cisplatin and gemcitabine alone arm or if the results provide other important information regarding efficacy or safety that should be included in product labeling.

2. To conduct and submit the results of a review of all available Genentech and Roche safety databases and of literature reports characterizing the incidence and severity of adverse events involving the central nervous system reported in patients with CNS metastases receiving Avastin. If the safety update (described above) provides insufficient data to characterize the risks of administration of Bevacizumab in patients with CNS metastases in product labeling, Genentech will submit a description of the plan, including one or more protocols, for assessment of the risks of Bevacizumab use in patients with CNS metastases arising from colorectal cancer or non-squamous non-small cell lung cancer origin.

3. To conduct a study, addressing the principles discussed in the ICH-E14 guidance document that will assess the impact of bevacizumab on the QT interval. The study will collect replicate ECG measurements at baseline and at various timepoints correlating with drug exposure, e.g., C_{max} and steady state.

2 Table of Contents

3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Overview: Bevacizumab was approved in February 2004 for use in combination with intravenous (IV) 5-fluorouracil (5-FU)-based chemotherapy for first-line treatment of patients with metastatic carcinoma of the colon and rectum (mCRC). The purpose of the present submission is to provide a supplement to the BLA for Avastin for use in combination with platinum-based chemotherapy for first-line treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) other than predominant squamous histology. This sBLA is supported by one Phase II/III study (E4599) and one Phase II Study AVF0757g.

Pharmacokinetic (PK) data for bevacizumab are available from 8 clinical trials, in which Avastin was administered either as a single agent or in combination with chemotherapeutic agents in patients with solid tumors. These data were submitted in their entirety in the initial BLA (STN: BL125085/0) and have been previously reviewed. In the present submission, PK and pharmacodynamic (PD) data from Study AVF0757g in NSCLC was included and there was no PK component in Study E4599. The PK and PD results of Study AVF0757g were previously submitted to the initial BLA and included in the overall PK data analyses.

Mechanism of Action: Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

Single-Dose and Multiple-Dose PK Parameters: After receiving a single dose of Avastin at 7.5 mg/kg or 15 mg/kg, there was no difference in clearance or volume of distribution between 2 dose levels. The volume of distribution approximated subject plasma volume. The elimination half-life was approximately 11 days. Serum bevacizumab concentrations appeared to plateau by day 105 after once-every-three-week (Q3W) dosing regimen. Peak and trough concentrations appeared to be in proportion to the dose studied. For doses of 7.5 and 15 mg/kg on day 105, C_{max} was 267±55 and 601±160 μg/mL, and C_{min} was 73±43 and 135±48 μg/mL, respectively.

In Vivo Drug-Drug Interaction: In Study AVF0757g, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin (PC) had substantially lower paclitaxel exposure after four cycles of treatment (at day 63) than those at day 0, while patients receiving PC without Avastin had a greater paclitaxel exposure at day 63 than at day 0.

PK in Special Populations (Avastin Labeling): Based on a population PK analysis of 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The clearance of bevacizumab varied by body weight, by gender, and by tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger V_c (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. In a randomized study of 813 patients (Study 1), there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin as compared to females and patients with low tumor burden. The relationship between bevacizumab exposure and clinical outcomes has not been explored.

No formal clinical studies in patients with hepatic impairment, renal impairment or in pediatric populations were conducted.

Exposure-Response: The relationship between bevacizumab PK parameter estimates and time to disease progression was examined. The results show the association of PK parameters with the combined IRF (cavitation)/investigator assessments of time to disease progression. There appears to be a relationship between AUC of bevacizumab and median time to progression when Avastin was given with paclitaxel and carboplatin.

Immunogenicity: As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Infusion Reactions: In clinical studies, infusion reactions with the first dose of Avastin were uncommon (<3%) and severe reactions occurred in 0.2% of patients. Infusion reactions reported in the clinical trials and postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Adequate information on rechallenge is not available.

Adverse Events: Avastin labeling carries the following warnings: Avastin administration can result in the development of gastrointestinal (GI) perforation, wound dehiscence, in some instances resulting in fatality. Fatal pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and Avastin. The incidence of severe or fatal hemoptysis was 31% in patients with squamous histology and 2.3% in patients with NSCLC excluding predominant squamous histology. Patients with recent visible hemoptysis should not receive Avastin.

Benefit and Risks: The addition of Avastin to platinum-based chemotherapy followed by Avastin alone until progression resulted in a clinically and statistically significant improvement in survival, as reflected in the 20% decrease in the hazard of death for patients receiving the combination therapy compared with those receiving chemotherapy alone (hazard ratio=0.80). Corresponding improvements in progression-free survival (PFS) and objective response rate (ORR) were observed. Avastin contributed additional toxicity to standard platinum-based chemotherapy in the treatment of metastatic NSCLC in the first-line setting. The exclusion of patients with NSCLC classified as squamous-cell histology and a history of gross hemoptysis ($\geq$1/2 teaspoon) resulted in a rate of severe or fatal pulmonary hemorrhage of 2.3%. The results of the clinical trial support use of Avastin in combination with carboplatin and paclitaxel in previously untreated patients with metastatic NSCLC other than squamous-cell carcinoma as categorized by the predominant cell type.

Question-Based Review (QBR)

4.1 General Attributes

1. ***What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?***

Chemistry and Physical-Chemical Properties: Avastin® (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab is produced in a Chinese hamster ovary (CHO) mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and has a molecular weight of approximately 149 kilodaltons.

Formulation: Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of bevacizumab (25 mg/mL).

Avastin Formulation (25 mg/mL)

Ingredient	Amount	
Bevacizumab (active ingredient)	100 mg	400 mg
α,α-trehalose dihydrate (———)	240 mg	960 mg
Sodium phosphate (monobasic, monohydrate)	23.2 mg	92.8 mg
Sodium phosphate (dibasic, anhydrous)	4.8 mg	19.2 mg
Polysorbate 20	1.6 mg	6.4 mg
Water for Injection, USP	4 mL	16 mL
pH	6.2	6.2

b(4)

Mechanism of Action: Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

Indications: The approved indication is that Avastin, used in combination with intravenous 5-fluorouracil–based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

The proposed indication with this present efficacy supplement is that Avastin, in combination with paclitaxel and carboplatin is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous, non-small cell lung cancer.

***Dosage and Route of Administration*:**

Metastatic carcinoma of the colon or rectum - The recommended dose of Avastin is 5 mg/kg when used in combination with bolus-IFL, and 10 mg/kg when used in combination with FOLFOX4, given once every 2 weeks as an IV infusion until disease progression.

Non–small cell lung cancer - The recommended dose of Avastin is 15 mg/kg, given once every 3 weeks as an IV infusion until disease progression.

The initial Avastin dose should be delivered over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Avastin therapy should not be initiated for at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of Avastin.

Dose modifications - There are no recommended dose reductions for the use of Avastin. If needed, Avastin should be either discontinued or temporarily suspended as described below.

Avastin should be permanently discontinued in patients who develop gastrointestinal perforation, wound dehiscence requiring medical intervention, serious bleeding, a severe arterial thromboembolic event, nephrotic syndrome, or hypertensive crisis.

Temporary suspension of Avastin is recommended in patients with evidence of moderate to severe proteinuria pending further evaluation and in patients with severe hypertension that is not controlled with medical management. The risk of continuation or temporary suspension of Avastin in patients with moderate to severe proteinuria is unknown.

Avastin should be suspended at least several weeks prior to elective surgery. Avastin should not be resumed until the surgical incision is fully healed.

2. ***What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?***

This sBLA is supported by the efficacy and safety demonstrated in a randomized, controlled, multicenter Phase II/III study (E4599) entitled, "*Randomized Phase II/III Trial of Paclitaxel plus Carboplatin with or without Bevacizumab in Patients with Advanced Nonsquamous NSCLC*" that was conducted by the National Cancer Institute (NCI) under IND 7921. It is also supported by Study AVF0757g, "*A Phase II, Multidose, Randomized, Multicenter Clinical Trial to Evaluate the Efficacy, Safety,*

Pharmacokinetics, and Pharmacodynamics of Recombinant Humanized Monoclonal Anti-VEGF Antibody (rhuMAb VEGF) Combined with Carboplatin and Paclitaxel Chemotherapy in Subjects with Locally Advanced or Metastatic (Stage IIIB or IV) Non-Small Cell Lung Cancer", conducted by Genentech under BB-IND 7023.

Pharmacokinetic (PK) data for bevacizumab are available from 8 clinical trials (see Table 1), in which Avastin was administered either as a single agent or in combination with chemotherapeutic agents in patients with solid tumors. These data were submitted in their entirety in the initial BLA (STN: BL125085/0) and have been previously reviewed. In the present submission, PK and pharmacodynamic (PD) data from Study AVF0757g in NSCLC was included and there was no PK component in Study E4599. The PK and PD results of Study AVF0757g were previously submitted to the initial BLA and included in the overall PK data analyses.

Table 1
Summary of Studies of Bevacizumab Providing Pharmacokinetic and Pharmacodynamic Data

	Study, Indication	Regimen			Concomitant Chemotherapy	Sampling Scheme Frequency
		Dose (mg/kg)	Frequency	Dose (mg/kg/wk)		
Phase I	AVF0737g Dose-escalation, solid tumors	0.1, 0.3, 1, 3, 10	Once, then 28 days later, weekly × 3	Varied	None (single agent)	Full profile for all subjects [a]
	AVF0761g, Solid tumors	3	Weekly	3	Doxorubicin, carboplatin/paclitaxel, 5-FU/LV	Full profile for all subjects [a]
Phase II	AVF0775g Pilot in HRPC	10	Every 2 weeks	5	None (single agent)	Multiple peaks and troughs for all subjects
	AVF0776g Dose-escalation, MBC	3, 10, 20	Every 2 weeks	1.5, 5, 10	None (single agent)	Multiple peaks and troughs for all subjects
	AVF0757g Combination, NSCLC	7.5, 15	Every 3 weeks	2.5, 5	Carboplatin/paclitaxel	Multiple peaks and troughs for all subjects
	AVF0780g Combination, CRC	5, 10	Every 2 weeks	2.5, 5	5-FU/LV	Multiple peaks and troughs all subjects
Phase III	AVF2119g MBC	15	Every 3 weeks	5	Capecitabine	Multiple peaks and troughs for a subset of subjects
	AVF2107g (Arm 2 and 3) CRC	5	Every 2 weeks	2.5	5-FU/LV/irinotecan, 5-FU/LV	Peaks and troughs at 2 cycles for a subset of subjects

5-FU=5-fluorouracil; CRC=colorectal carcinoma; HRPC=hormone refractory prostate carcinoma; LV=leucovorin; MBC=metastatic breast carcinoma; NSCLC=non small cell lung carcinoma.

[a] Serial samples collected over 1 month after administration of either first or last dose.

4.2 General Clinical Pharmacology

1. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

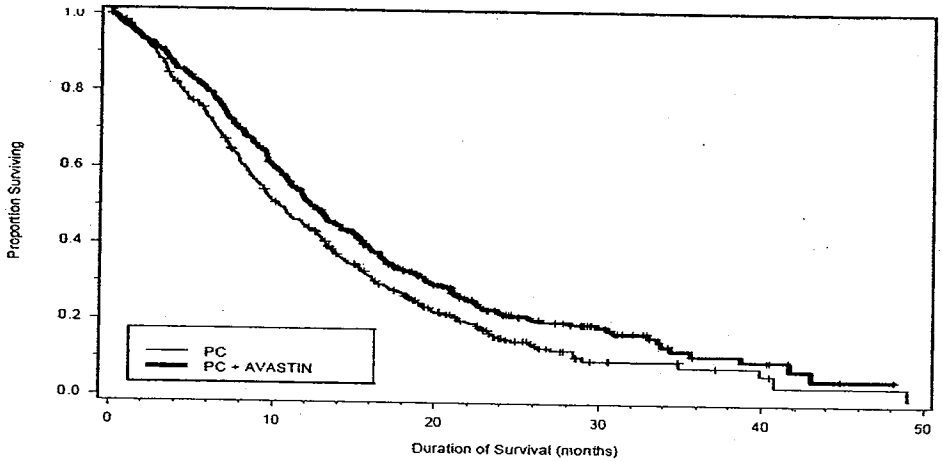
Response Endpoints: The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study (Study 4599, n=878), supported by a randomized, dose ranging, active controlled Phase II study (Study AVF0757g, n=98).

In Study 4599, chemotherapy-naïve patients with locally advanced, metastatic or recurrent non-squamous NSCLC were randomized (1:1) to receive six cycles of paclitaxel 200 mg/m^2 and carboplatin AUC=6.0, both by IV infusion on day 1 (PC) or

PC in combination with Avastin at a dose of 15 mg/kg by IV infusion on day 1 (PC plus Avastin). Cycles were repeated every 21 days. Patients with predominant squamous histology (mixed cell type tumors only), central nervous system (CNS) metastasis, gross hemoptysis (≥1/2 tsp of red blood), or unstable angina and those receiving therapeutic anticoagulation were excluded. The main outcome measure of the study was duration of survival.

Among the 878 patients randomized to the two treatment arms, the median age was 63, 46% were female, 43% were ≥age 65, and 28% had ≥5% weight loss at study entry. Eleven percent had recurrent disease and of the remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease. The survival curves are presented in Figure 1. Overall survival (OS) was statistically significantly higher among patients receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs. 10.3 months (repeated 95% CI 0.68, 0.94; final p value 0.013, stratified log-rank test, HR =0.80).

Figure 1. Duration of Survival in Study 4599



In an exploratory analysis across patient subgroups, the impact of Avastin on overall survival was less robust in the following: women [HR = 0.99 (95% CI: 0.79, 1.25)], age ≥65 years [HR = 0.91 (95% CI: 0.72, 1.14)] and patients with ≥5% weight loss at study entry [HR = 0.96 (95% CI: 0.73, 1.26)].

Safety: Avastin labeling carries the following warnings: Avastin administration can result in the development of gastrointestinal (GI) perforation, in some instances resulting in fatality. GI perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with Avastin (i.e., was not correlated to duration of exposure). In incidence of GI perforation (GI perforation, fistula formation, and/or intra-abdominal abscess) in patients with colorectal cancer and in patients with NSCLC receiving Avastin was 2.4% and 0.9%, respectively. Avastin therapy should be permanently discontinued in patients with GI perforation.

Avastin administration can result in the development of wound dehiscence, in some instance resulting fatality. Avastin therapy should be permanently discontinued in

patients with wound dehiscence requiring medical intervention. The appropriate interval between termination of Avastin and subsequent elective surgery required to avoid the risks of impaired wound healing/wound dehiscence has not been determined.

Fatal pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and Avastin. The incidence of severe or fatal hemoptysis was 31% in patients with squamous histology and 2.3% in patients with NSCLC excluding predominant squamous histology. Patients with recent visible hemoptysis should not receive Avastin.

Arterial thromboembolic events (ATE) occurred at a higher incidence in patients receiving Avastin in combination with chemotherapy as compared to those receiving chemotherapy alone. ATE included cerebral infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), angina, and a variety of other ATE. These events were fatal in some instances. In a pooled analysis of randomized, controlled clinical trials involving 1745 patients, the incidence of ATE was 4.4% among patients treated with Avastin in combination with chemotherapy and 1.9% among patients receiving chemotherapy alone. Fatal outcomes for these events occurred in 7 of 963 patients (0.7%) who were treated with Avastin in combination with chemotherapy, compared to 3 of 782 patients (0.4%) who were treated with chemotherapy alone. The incidences of both cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial events (2.1% vs. 1.0%) were increased in patients receiving Avastin compared to chemotherapy alone. The relative risk of ATE was greater in patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).

The incidence of severe hypertension was increased in patients receiving Avastin as compared to controls. Across clinical studies the incidence of NCI-CTC Grade 3 or 4 hypertension ranged from 8–18%. Medication classes used for management of patients with Grade 3 hypertension receiving Avastin included angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers. Development or worsening of hypertension can require hospitalization or require discontinuation of Avastin in up to 1.7% of patients. Hypertension can persist after discontinuation of Avastin. Complications can include hypertensive encephalopathy and CNS hemorrhage.

In the post-marketing experience, acute increases in blood pressure associated with initial or subsequent infusions of Avastin have been reported. Some cases were serious and associated with clinical sequelae. Permanently discontinue Avastin in patients with hypertensive crisis. Temporarily suspend Avastin in patients with severe hypertension that is not controlled with medical management.

The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to control. In Studies 1, 3 and 5, the incidence of NCI-CTC Grade 3 and 4 proteinuria, characterized as >3.5 gm/24 hours, ranged up to 3.0% in Avastin-treated patients. Nephrotic syndrome occurred in seven of 1459 (0.5%) patients receiving Avastin in clinical studies. One patient died and one required dialysis. In three patients, proteinuria decreased in severity several months after discontinuation of Avastin. No

patient had normalization of urinary protein levels (by 24-hour urine) following discontinuation of Avastin.

The highest incidence of proteinuria was observed in a dose-ranging, placebo-controlled, randomized study of Avastin in patients with metastatic renal cell carcinoma, an indication for which Avastin is not approved; 24-hour urine collections were obtained in approximately half the patients enrolled. Among patients in whom 24-hour urine collections were obtained, four of 19 (21%) patients receiving Avastin at 10 mg/kg every two weeks, two of 14 (14%) patients receiving Avastin at 3 mg/kg every two weeks, and none of the 15 placebo patients experienced NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

Discontinue Avastin in patients with nephrotic syndrome. The safety of continued Avastin treatment in patients with moderate to severe proteinuria has not been evaluated. In most clinical studies, Avastin was interrupted for ≥2 grams of proteinuria/24 hours and resumed when proteinuria was <2 gm/24 hours. Patients with moderate to severe proteinuria based on 24-hour collections should be monitored regularly until improvement and/or resolution is observed.

Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left ventricular dysfunction, was reported in 25 of 1459 (1.7%) patients receiving Avastin in clinical studies. The risk of CHF appears to be higher in patients receiving Avastin who have received prior or concurrent anthracyclines. In a controlled study in patients with breast cancer (an unlabelled indication), the incidence of CHF was higher in the Avastin plus chemotherapy arm as compared to the chemotherapy alone arm. Congestive heart failure occurred in 13 of 299 (4%) patients who received prior anthracyclines and/or left chest wall irradiation. Congestive heart failure occurred in six of 44 (14%) patients with relapsed acute leukemia (an unlabelled indication) receiving Avastin and concurrent anthracyclines in a single arm study. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

Benefit and Risks: The addition of Avastin to platinum-based chemotherapy followed by Avastin alone until progression resulted in a clinically and statistically significant improvement in survival, as reflected in the 20% decrease in the hazard of death for patients receiving the combination therapy compared with those receiving chemotherapy alone (hazard ratio=0.80). Corresponding improvements in PFS and objective response rate were observed. Avastin contributed additional toxicity to standard platinum-based chemotherapy in the treatment of metastatic NSCLC in the first-line setting. The exclusion of patients with NSCLC classified as squamous-cell histology and a history of gross hemoptysis (≥1/2 teaspoon) resulted in a rate of severe or fatal pulmonary hemorrhage of 2.3%. The results of the clinical trial support use of Avastin in combination with carboplatin and paclitaxel in previously untreated patients with metastatic NSCLC other than squamous-cell carcinoma as categorized by the predominant cell type.

2. ***Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship? (if yes, refer to IV, F, Analytical Section; if no, describe the reasons)***

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF). The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand).

3. ***What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?***

Exposure-Response: The relationship between bevacizumab PK parameter estimates and time to disease progression was examined. Table 2 shows the association of PK parameters with the combined IRF (cavitation)/investigator assessments of time to disease progression. The statistically significance of the association of CL, AUC_{inf}, and volume of distribution with time to disease progression was indicated.

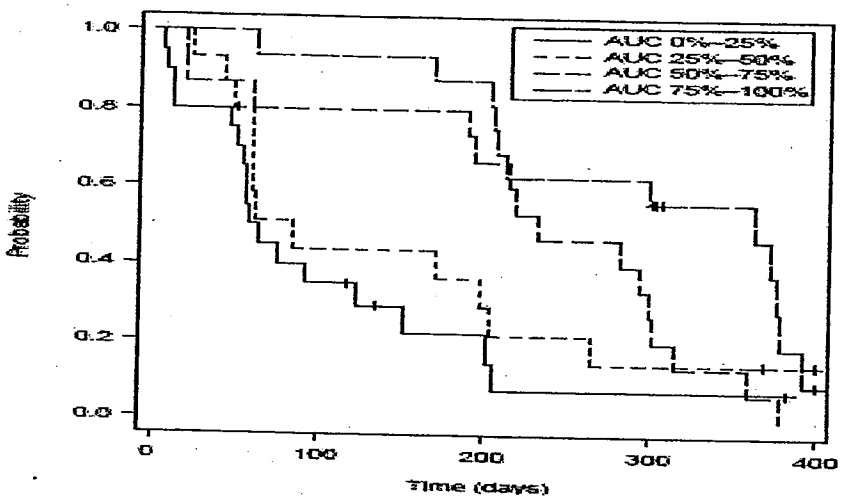
Table 2
Log-Rank Test of the Association of Pharmacokinetic Parameters with Time to Disease Progression (IRF [Cavitation]/Investigator Assessment)

Variable	Strata	Median Time to Progression (days)	p-value
AUC_{inf}	>4050 µg/mL•day	293.0	0.0059
	≤4050 µg/mL•day	84.0	
CL	>2.56 mL/kg/day	92.0	0.0018
	≤2.56 mL/kg/day	219.0	
C_{max}	>270 µg/mL	233.0	0.1721
	≤270 µg/mL	171.0	
k_{10}	>0.0629 /day	152.0	0.2804
	≤0.0629 /day	207.0	
Vol	>39.3 mL/kg	171.0	0.0459
	≤39.3 mL/kg	213.0	

AUC_{inf} = area under the curve from 0 to infinity for 1 dosing interval; CL = systemic clearance; C_{max} = model predicted maximum concentration after the first dose; k_{10} = elimination rate constant; Vol = volume of distribution.

The relationship between AUC_{inf} and time to disease progression (IRF [cavitation]/ investigator assessment) was evaluated by dividing the AUC_{inf} values into quartiles (AUC_{inf}<2875, AUC_{inf}=2875-4050, AUC_{inf}=4050–6075, and AUC_{inf}>6075 µg/mL•day) and then plotting time to disease progression for each quartile (Figure 2).

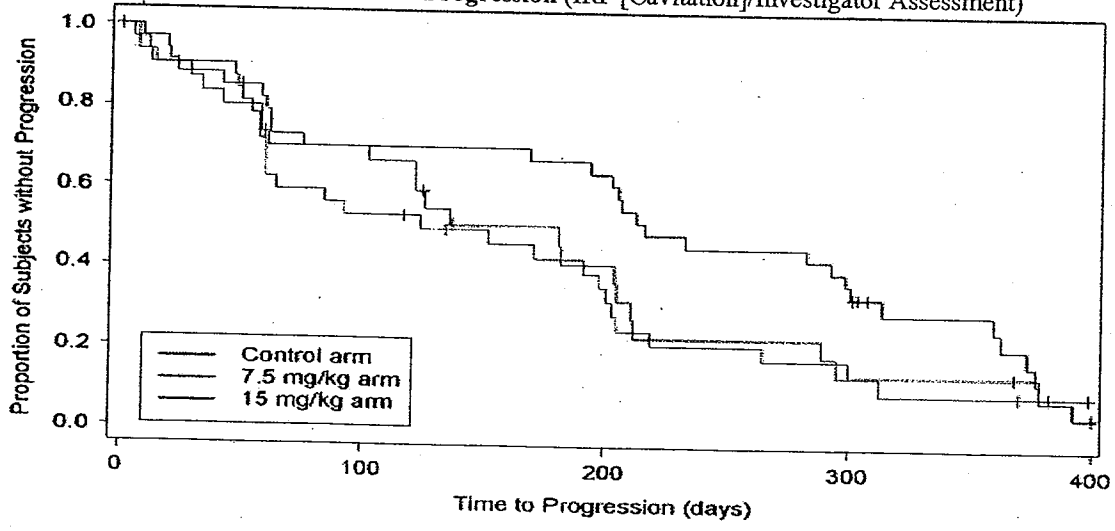
Figure 2. Time to Disease Progression by AUC (IRF [Cavitation]/Investigator Assessment)



In subjects with an AUC_{inf} greater than the median of 4050 µg/mL•day, the median time to disease progression (IRF [cavitation]/investigator assessment) was 293 days (203–373 days, 25%–75%), whereas in subjects with an AUC_{inf} less than the median AUC_{inf}, the median time to disease progression was 84 days (57–201 days, 25%–75%). An AUC_{inf} of >4050 µg/mL•day was observed in 27 of 32 subjects (84.4%) in the 15 mg/kg arm. Note that the strong association of baseline albumin with both clearance and time to disease progression suggests that drug exposure may be related to health status; thus the direct relationship between the pharmacokinetics and time to disease progression should be interpreted with caution.

Dose-Response: Time to disease progression was the primary efficacy endpoint in Study AVF0757g. Figure 3 present the Kaplan-Meier curve for IRF (cavitation) /investigator assessment.

Figure 3. Time to Disease Progression (IRF [Cavitation]/Investigator Assessment)



A number of imbalances in demographic and baseline characteristics were observed (sex, ECOG performance status of 0, disease duration of <1 year, squamous cell histology, cancer stage and prior cancer treatment. A multivariate Cox regression model was fit to assess the impact of these factors on the estimate of treatment effect by IRF (cavitation)/investigator-assessed time to disease progression (Table 3). After adjusted for sex, ECOG performance status, and baseline albumin, the estimated reduction in the hazard of progression for the 15 mg/kg arm was 47%, with a 95% CI of 6% to 71%. The 7.5 mg/kg arm was not statistically significant compared with the control arm.

Table 3
Estimate of Treatment Effect after Adjusting for Sex, ECOG Performance Status, and Baseline Albumin

Model Terms [a]	Hazard Ratio	95% Confidence Interval	p-value
7.5 mg/kg	0.760	(0.429, 1.35)	0.35
15 mg/kg	0.523	(0.291, 0.938)	0.030
Female sex	1.772	(1.05, 2.98)	0.031
ECOG status of 0	0.642	(0.384, 1.07)	0.091
Log_{10} (baseline albumin)			<0.001

[a] Likelihood ratio test = 33.18 on 5 df; p<0.001, n=97.
(Two observations were deleted because of missing data.)

The results of tumor evaluations (response rates) performed by the investigators and the IRF are presented in Table 4. These assessments found an improvement in the confirmed response rate in the 15 mg/kg arm compared with the control arm. Fisher's exact test for the comparison of investigator-assessed response rate in the 15 mg/kg arm versus the control arm yielded a two-sided p-value of 0.27.

Table 4
Confirmed Response Rates

Source	Control (N=32)	7.5 mg/kg (N=32)	15 mg/kg (N=35)
Investigator	6 (18.8%)	9 (28.1%)	11 (31.5%)
IRF/investigator	10 (31.3%)	7 (21.9%)	14 (40.0%)
IRF (cavitation)/investigator	10 (31.3%)	8 (25.0%)	18 (51.4%)

The median survival time for the thee treatment arms are presented in Table 5. Note that median survival has not been reached in the 15 mg/kg arm because fewer than half of the patients in that arm have died.

Table 5
Survival Time

	Control (N=32)	7.5 mg/kg (N=32)	15 mg/kg (N=34)
Deaths	17	18	15
Censored observations	15	14	19
Survival time (days)			
Median	403.0 [a]	352.0	436.0 [a]
25%–75% percentile	163.0–572.0	205.5– .	230.0– .
Minimum–maximum	5.0–572.0	7.0–468.0 [b]	23.0–446.0 [b]
95% CI (median)	(213.0, 572.0)	(284.0, .)	(348.0, .)
p-value (log rank)	NA	0.7236	0.6389

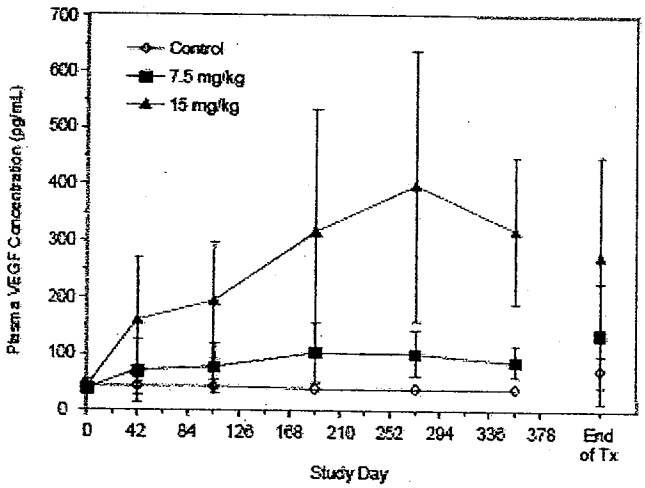
NA = not applicable. A dot indicates that the value could not be estimated.
[a] Estimate subject to change based on additional survival follow-up.
[b] Observation censored.

The median duration of objective response by combined IRF (cavitation)/investigator assessment was 159 days in the control arm, 154 days in the 7.5 mg/kg arm, and 249 days in the 15 mg/kg arm.

Response by Histology: Because of the life-threatening hemorrhages seen in this study and the possibility that squamous cell histology is a co-risk factor with Avastin for these hemorrhages, the possibility of excluding patients with squamous cell histology from future clinical trials of Avastin was considered. Treatment with Avastin appeared to increase time to disease progression and response rates in patients without squamous cell histology. Survival also appeared to be improved in this subgroup after adjustments for sex and baseline albumin.

VEGF Pharmacokinetic Parameters for Each Subject: At baseline, plasma samples for 4 of 78 subjects were above the assay limit of quantification of 40 pg/mL; the VEGF levels of the remaining 74 subjects were below the detectable limit. In 16 subjects, the sample drawn at baseline was collected as serum. Since it is known that platelets can release VEGF during coagulation (Webb et al. 1998), the serum results were excluded from the analysis. Figure 4 shows the mean VEGF concentration–time profile.

Figure 4. Mean Plasma VEGF Concentration–Time Profiles



The data points presented in the figure represent average plasma VEGF levels for subjects remaining on study at each corresponding timepoint.

An increase in total plasma VEGF concentration was observed in both Avastin arms, with average maximum concentrations of 130±87.3 and 325±215 pg/mL for the 7.5 and 15 mg/kg arms, respectively. This corresponds to an average 3- and 7-fold increase in plasma VEGF levels over baseline for the 7.5 and 15 mg/kg arms, respectively. VEGF exposure was evaluated by calculating the VEGF $AUC_{0\text{-}Tlast}/T_{last}$ for all subjects. An increase in VEGF exposure was seen in both Avastin arms (Table 6).

Table 6
Plasma VEGF PK Parameters following Avastin Administration (Arithmetic Mean ± SD)

Arm	C_{max} (pg/mL)	C_{max}/C_0	$AUC_{0-Tlast}/T_{last}$ (pg/mL)
Control	51.9±37.1 n=20	1.24±0.981 n=17	43.8±13.6 n=20
7.5 mg/kg	130±87.3 n=25	3.13±2.28 n=21	81.0±44.1 n=25
15 mg/kg	325±215 n=31	7.34±4.22 n=28	198±114 n=31

$AUC_{0-Tlast}/T_{last}$ = plasma VEGF concentration–time curve from baseline to the time of the last plasma sample, divided by the time of the last plasma sample; C_{max} = maximum drug concentration observed in plasma; C_{max}/C_0 = maximum drug concentration divided by baseline drug concentration.

Increases in VEGF concentration have been observed in previous clinical trials and are most likely due to decreased VEGF clearance when bound to bevacizumab, as demonstrated in a nonclinical study (Gaudreault and Hsei 2000).

a) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Avastin was given to patients with solid tumors at doses of 0.1, 0.3, 1, 3, and 10 mg/kg as a single dose and then 28 days later weekly for 3 more doses in a Phase 1 study (AVF0737g). The pharmacokinetics of bevacizumab was linear between 1 to 10 mg/kg (from the BLA review).

b) Do PK parameters change with time following chronic dosing?

No. PK parameters did not change with time following chronic dosing. Following four doses of Avastin, the clearance of bevacizumab after all four doses and after the first dose was comparable (from the BLA review).

c) How long is the time to the onset and offset of the pharmacological response or clinical endpoint?

Overall survival was statistically significantly higher among patients receiving paclitaxel/carboplatin (PC) plus Avastin compared with those receiving PC alone (nominal p value 0.012, stratified log-rank test, HR =0.81).

d) Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

None.

4. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetic information for intravenously administered Avastin submitted in this application was obtained from cancer patients. No studies were conducted in healthy volunteers.

a) What are the basic PK parameters?

Avastin Alone (From BLA review): A Phase I, open-label, dose-escalation PK study of Avastin without concomitant therapy was conducted in subjects with advanced malignancies (study # AVF0737g). Five doses of Avastin (0.1, 0.3, 1.0, 3.0, and 10 mg/kg) were evaluated in this trial and five subjects were enrolled at each dose level. Blood samples were collected for 28 days following administration of the first dose, for 8 hours after each dose on days 28 and 35, and for 30 days after administration of the last dose on day 42. Table 7 summarizes the PK parameters of Avastin administered to patients following IV infusion.

Table 7

Selected Compartmental Pharmacokinetic Parameters following IV Infusion of Bevacizumab in Study AVF0737g (Mean±SD)

Dose (mg/kg)	n	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} (mL/kg)	$t_{1/2}$ initial [a] (days)	$t_{1/2}$ terminal [b] (days)	MRT (days)
0.1	5	9.29±7.07	48.0±17.4	50.1±17.0	NA	5.21±2.41	7.40±3.44
0.3	5	5.07±2.39	48.6±13.0	60.3±7.30	1.9	10.4±5.34	13.9±6.11
1.0	5	3.27±0.81	37.9±7.77	60.4±18.8	1.30±0.535	14.7±6.92	19.9±9.25
3.0	4	3.65±2.10	41.4±12.0	53.4±12.0	0.844	12.8±6.60	18.1±9.36
10	5	2.75±0.47	43.5±12.6	53.0±10.9	2.17	14.2±3.36	19.3±3.18

The clearance of bevacizumab appears to decrease with increasing dose. Volume of distribution of the central compartment (Vc) and at steady state ranged from 37.9 to 48.0 mL/kg and 50.1 to 60.4 mL/kg, respectively. Both volumes were independent of the dose given to the patients. The half-life of bevacizumab was approximately 14 to 15 days by the compartmental analysis. A non-compartmental analysis indicated that half-life after single and multiple doses ranged from 13 to 20 days (Table 8).

Table 8
Terminal Half-Life Estimates in Study AVF0737g by Non-Compartmental Methods (Mean±SD)

Dose (mg/kg)	Terminal Half-Life (days)		
	First Dose (n)	Fourth Dose (n)	Mean of First and Fourth Doses (n)
1	12.5±4.05 (5)	14.4±5.56 (5)	13.4±4.69 (10)
3	18.1±6.49 (5)	19.4±11.3 (4)	18.7±8.33 (9)
10	14.3±2.45 (5)	20.2±8.37 (5)	17.3±6.59 (10)

Following multiple dosing no accumulation of drug was noted and the PK of bevacizumab was similar following single and multiple dosing (Table 9 and Figure 5).

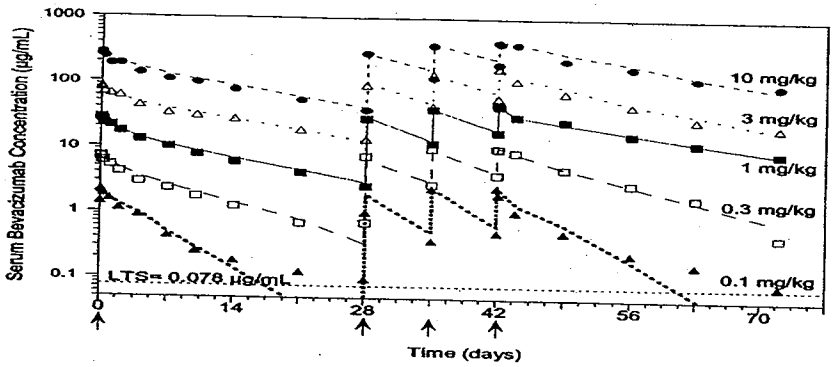
Table 9

Bevacizumab Pharmacokinetic Parameters Estimated Using First-Dose Data and All Available Data in Study AVF0737g (Mean±SD)

Dose (mg/kg)	n	CL (mL/day/kg)		V_c (mL/kg)	
		First Dose	All Data	First Dose	All Data
0.1	5	9.13±6.90	9.29±7.07	44.9±16.5	48.0±17.4
0.3	5	5.50±2.47	5.07±2.39	47.1±11.5	48.6±13.0
1.0	5	3.55±0.716	3.27±0.811	37.8±8.85	37.9±7.77
3.0	4	3.45±1.82	3.65±2.10	40.6±11.4	41.4±12.0
10	5	2.81±1.14	2.75±0.472	41.1±9.19	43.5±12.5

Figure 5

Mean Bevacizumab Concentration–Time Profiles in Study AVF0737g



Bevacizumab disposition was similar when administered either as a single dose or as multiple doses. The Sponsor's comparison however, is not appropriate. The Sponsor should have compared the PK data after the first dose and the last dose, rather than comparing the first dose with the all four doses.

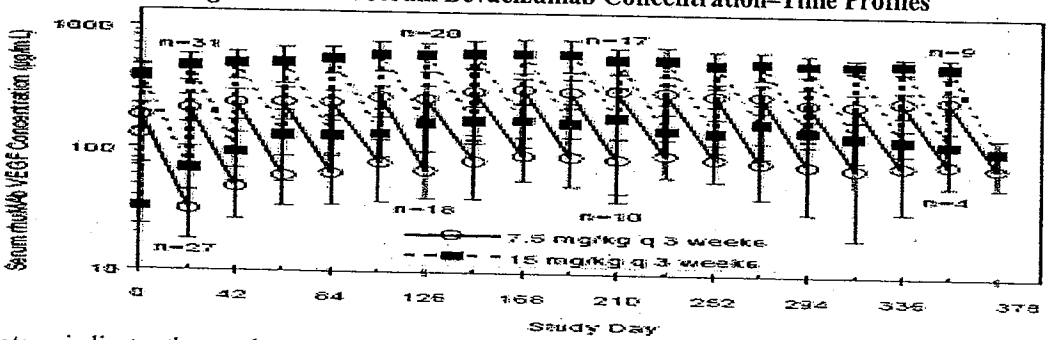
Table 10
Accumulation Index of Bevacizumab

Study	Dose (mg/kg)	Dose Frequency	Average $C_{trough,\ first}$ (µg/mL)	No. of Subjects with $C_{trough,\ first}$	Average $C_{trough,\ last}$ (µg/mL)	T_{last} (day)	No of Subjects with $C_{trough\ last}$	Accumulation Index	Expected Accumulation Index
AVF0775g	10	q 2 wk	67.1	15	182	182	5	2.7	2.6
AVF0776g	3	q 2 wk	55.5	16	78.4	154	3	1.4	2.6
	10	q 2 wk	79.4	41	229.6	154	8	2.9	2.6
	20	q 2 wk	137.5	16	332.3	154	3	2.4	2.6
AVF0780g	5	q 2 wk	35.4	32	81.7	322	11	2.3	2.6
	10	q 2 wk	59.9	30	169.2	322	10	2.8	2.6
AVF0757g	7.5	q 3 wk	31.3	27	58.3	378	4	1.9	1.9
	15	q 3 wk	68.4	31	107.9	378	7	1.6	1.9

C_{trough}=trough concentration.

Avastin in Combination with Chemotherapy (Study AVF0757g): A total of 67 NSCLC patients were randomized to one of the two Avastin arms. Of the 67 subjects randomized, 66 received at least one dose of Avastin and 62 had enough serum bevacizumab samples to perform a one-compartment analysis. Mean bevacizumab concentration versus nominal time profiles are presented in Figure 6.

Figure 6. Mean Serum Bevacizumab Concentration–Time Profiles



Note: n indicates the number of subjects in each of the two Avastin arms on Days 21, 126, 210, and 357.

Serum bevacizumab concentrations appeared to plateau by day 105. On day 105, peak concentrations were 267±55 and 601±160 µg/mL, and trough levels were 73±43 and 135±48 µg/mL for the 7.5 and 15 mg/kg arms, respectively (mean ± standard deviation). C_{min} and Cmax appeared to be in proportion to the doses studied. Pharmacokinetic parameter estimates are presented in Table 11.

Table 11
Serum Bevacizumab Pharmacokinetic Parameters following Avastin Administration (Arithmetic Mean ± SD)

Arm	AUC_{inf} (µg/mL·day)	CL (mL/kg/day)	Vol (mL/kg)	$t_{1/2}$ (day)	MRT (day)
7.5 mg/kg (n=30)	2950±1085	2.98±1.39	42.9±9.1	11.2±3.55	16.2±5.12
15 mg/kg (n=32)	6162±1897	2.75±1.16	39.4±8.69	10.7±2.64	15.5±3.81

AUC_{inf} = Area under the curve from t = 0 to infinity for first dosing interval; CL = systemic clearance; Vol = volume of distribution; t1/2 = elimination half-life; MRT = mean residence time.

There was no difference in clearance or volume of distribution between the two Avastin arms. The volume of distribution approximated subject plasma volume (mean ± SD) for both arms.

*5. **What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?***

The integrated PK analysis investigated the inter-individual variability associated with the PK data. The interpatient variability in the PK parameter estimates ranged from 20% to 50%.

4.3 Intrinsic Factors

*1. **What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?***

Pharmacokinetics in Special Populations (from the BLA review): No formal clinical studies in patients with hepatic impairment, renal impairment or in pediatric populations were conducted. A population PK analysis was conducted to investigate the potential effects of selected covariates including, age, gender, race, height, body weight, body surface area, and lean body weight, creatinine clearance, alkaline phosphatase, serum glutamic oxaloacetic transferase concentration, serum glutamic transaminase concentration, total bilirubin, total protein, albumin, serum creatinine, and combination chemotherapy.

The population PK analysis for bevacizumab was based on the pooled datasets from eight clinical studies including two Phase I studies, four Phase II studies, and two Phase III studies in subjects with several types of solid tumors. The analysis included a total of

4629 bevacizumab concentrations for 491 subjects who received IV infusion doses weekly, every 2 weeks, or every 3 weeks at doses ranging from 1 to 20 mg/kg. In all studies, Avastin was administered initially as a 90-minute infusion. If this first infusion was well tolerated, the infusion duration could be decreased in increments of 30 minutes. The infusion duration was not to be shorter than 30 minutes. The studies included in the analysis are summarized in Table 12.

Table 12

Summary of studies included in population PK study

Study	Bevacizumab Dose (mg/kg)	Dosing Frequency	Concomitant Chemotherapy	Sampling Scheme Frequency	Subjects with PK Data
Phase I					
AVF0737g: Dose-escalation, solid tumors	1, 3, 10[a]	Once monthly, then weekly for 3 weeks	Single agent	Full profile[b]	25
AVF0761g: Solid tumors	3	Weekly	Doxorubicin, carboplatin/paclitaxel, 5-FU/LV	Full profile[b]	12
Phase II					
AVF0775g: Pilot in HRPC	10	Every 2 weeks	Single agent	Multiple peaks and troughs	15
AVF0776g: Dose-escalation, MBC	3, 10, 20	Every 2 weeks	Single Agent	Multiple peaks and troughs	74
AVF0757g: Combination, NSCLC	7.5, 15	Every 3 weeks	Carboplatin/paclitaxel	Multiple peaks and troughs	66
AVF0780g: Combination, CRC	5, 10	Every 2 weeks	5-FU/LV	Multiple peaks and troughs	67
Phase III					
AVF2119g: MBC	15	Every 3 weeks	Capecitabine	Multiple peaks and troughs	38
AVF2107g: Combination, CRC	5	Every 2 weeks	5-FU/LV or 5-FU/LV/CPT-11	Peaks and troughs at 2 cycles	236

5-FU=5-fluorouracil; CRC=Colorectal carcinoma; HRPC=Hormone refractory prostate carcinoma; LV=Leucovorin; MBC=Metastatic breast carcinoma; NSCLC=Non small cell lung carcinoma, CPT-11=Irinotecan.

[a] Doses of 0.1 and 0.3 mg/kg that were also investigated in this study in 10 patients were not included in the analysis because bevacizumab clearance at these doses was faster and these doses were not evaluated in further studies.

[b] Serial samples collected over 1 month after administration of either first or last dose.

In the final model, of the 17 covariates tested, body weight, gender, albumin, alkaline phosphatase, SGOT, and chemotherapy were the covariates that were significantly associated with bevacizumab disposition (Table 13).

Table 13

Summary of Population Parameters with CV (%) for the Final PP Model and Final Model

Parameter	Final PP Model	Final Model (δ=−62.7)	Final Model FOCE	Final Model with CL–V_c Correlation (δ=−33.3)
MOF	37317.7	37255.0	37204.1	37221.7
Typical CL (L/day)	0.185 (4.0)	0.207 (4.6)	0.212 (4.3)	0.208 (4.6)
GDR on CL	0.235 (30.9)	0.264 (27.6)	0.269 (25.9)	0.268 (27.7)
WT on CL	0.370 (36.8)	0.368 (36.7)	0.378 (36.8)	0.353 (38.2)
ALBU on CL	−0.736 (20.5)	−0.726 (20.7)	−0.765 (20.4)	−0.739 (20.3)
ALK on CL	0.132 (30.8)	0.133 (26.4)	0.143 (26.4)	0.131 (26.3)
SGOT on CL	−0.0658 (55.8)	−0.0715 (48.5)	−0.0625 (57.3)	−0.0756 (46.3)
CHEM on CL (0 vs. 5)	NA	−0.003 (1630.5)	0.0281 (175)	−0.0112 (398)
CHEM on CL (1–4 vs. 5)	NA	−0.174 (22.1)	−0.179 (23.3)	−0.180 (21.1)
Typical V_c (L)	2.69 (1.8)	2.66 (1.7)	2.68 (1.6)	2.65 (1.6)
GDR on V_c	0.215 (13.4)	0.221 (13.2)	0.215 (12.8)	0.210 (13.7)
WT on V_c	0.413 (13.4)	0.411 (13.6)	0.408 (14.0)	0.410 (12.7)
ALBU on V_c	−0.341 (17.2)	−0.333 (17.2)	−0.329 (17.8)	−0.306 (19.0)
K_{12} (day^{-1})	0.214 (28.7)	0.223 (27.9)	0.264 (25.5)	0.205 (28.9)
K_{21} (day^{-1})	0.200 (24.0)	0.215 (22.9)	0.262 (20.7)	0.201 (23.7)
ω_{CL} (%)	24.1 (11.8)	26.0 (14.0)	26.8 (15.8)	25.6 (14.1)
ω_{Vc} (%)	17.1 (15.2)	16.8 (14.2)	16.3 (13.0)	16.1 (13.3)
Correlation (η_{Vc}, η_{CL})	NA	NA	NA	0.39
σ_{prop} (%)	17.5 (9.0)	17.2 (8.4)	17.3 (8.3)	17.1 (8.4)
σ_{add} (µg/mL)	7.6 (56.3)	7.2 (60.8)	7.0 (63.0)	7.3 (59.8)
K_{10} (day^{-1})	0.0688	0.0779	0.0792	0.0786
$t_{1/2\alpha}$ (days)	1.53	1.44	1.22	1.54
$t_{1/2\beta}$ (days)	22.8	19.9	19.0	19.7

Based on the final model (chosen based on the minimum objective function), clearance was 0.262 and 0.207 L/day for a typical male and female subject, respectively. The volume of distribution of the central compartment (V_c) was 3.25 and 2.66 L in male and female subjects, respectively. The estimated half-life was approximately 20 days. Body weight was an important covariate affecting bevacizumab CL and volume. There was no correlation between bevacizumab clearance and age. Gender seems to have impact on clearance and volume. The clearance and volume is 21% and 18% lower in the females than the males, respectively. After correcting for body weight, male subjects had a higher bevacizumab clearance (26%) and a larger Vc (22%) than females. However, this difference may not be of any clinical significance.

2. ***Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.***

a) ***Elderly***

In the population PK analysis, there was no correlation between bevacizumab clearance and age. In Study AVF 0757g, when subjects were compared by age, either above or below the median age of 62.5 years, there was no difference in clearance or volume of distribution.

In an exploratory analysis across patient subgroups in Study 4599, the impact of Avastin on overall survival was less robust in patients with age ≥65 years [HR = 0.91 (95% CI: 0.72, 1.14)].

In Study 4599, patients age 65 and older receiving paclitaxel/carboplatin plus Avastin had a greater relative risk for proteinuria as compared to younger patients. Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients age 65 or older and 1127 patients less than 65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).

b) Pediatric Patients

The safety and effectiveness of Avastin in pediatric patients has not been studied. However, physeal dysplasia was observed in juvenile cynomolgus monkeys with open

growth plates treated for four weeks with doses that were less than the recommended human dose based on mg/kg and exposure. The incidence and severity of physeal dysplasia were dose-related and were at least partially reversible upon cessation of treatment (from Avastin Labeling).

c) Gender

In the population PK analysis, based on the final model (chosen based on the minimum objective function), gender seems to have an impact on clearance and volume. The clearance and volume is 21% (0.207 and 0.262 L/day) and 18% (2.66 and 3.25 L) lower in the females than the males. After correcting for body weight, male subjects had a higher bevacizumab clearance (26%) and a larger V_c (22%) than females. However, this difference may not be of any clinical significance. In Study AVF0757g, a sex difference was observed in clearance, with a mean clearance of 2.40±1.17 mL/kg/day in women and 3.24±1.25 mL/kg/day in men ($p<0.01$).

In an exploratory analysis across patient subgroups in Study 4599, the impact of Avastin on overall survival was less robust in women [HR = 0.99 (95% CI: 0.79, 1.25)].

d) *Race*

In the population PK analysis, race was not found to have an impact on bevacizumab exposure; however, race distribution was not captured in the BLA review.

e) Renal Impairment

No formal PK study has been conducted in patients with renal impairment. In the population PK analysis, creatinine clearance was not found to have an impact on bevacizumab exposure; however, population distribution with regard to renal function was not captured in the BLA review.

f) Hepatic Impairment

No formal PK study has been conducted in patients with hepatic impairment. In the population PK analysis, albumin, alkaline phosphatase, SGOT were found to be significantly associated with Bevacizumab exposure; however, population distribution with regard to hepatic function was not captured in the BLA review.

g) What pregnancy and lactation use information is there in the application?

Pregnancy Category C (from Avastin labeling): Avastin has been shown to be teratogenic in rabbits when administered in doses that approximate the human dose on an mg/kg basis. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions, and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested.

Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of Avastin is likely to result in adverse effects on pregnancy. There are no adequate and well-controlled studies in pregnant women. Avastin should be used during pregnancy or in any woman not employing adequate contraception only if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding

the potential risk of Avastin to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving Avastin, she should be apprised of the potential hazard to the fetus and/or the potential risk of loss of pregnancy. Patients who discontinue Avastin should also be counseled concerning the prolonged exposure following discontinuation of therapy (half-life of approximately 20 days) and the possible effects of Avastin on fetal development.

Nursing Mothers (from Avastin labeling): It is not known whether Avastin is secreted in human milk. Because human IgG1 is secreted into human milk, the potential for absorption and harm to the infant after ingestion is unknown. Women should be advised to discontinue nursing during treatment with Avastin and for a prolonged period following the use of Avastin, taking into account the half-life of the product, approximately 20 days [range 11–50 days].

h) Other factors that are important to understanding the drug's efficacy and safety
Univariate tests of association conducted in Study AVF0757g demonstrated that clearance is associated with sex, baseline ECOG status, baseline tumor area, and baseline serum albumin levels. A multivariate model indicated that baseline serum albumin is the strongest predictor of bevacizumab clearance among the variables examined.

Tumor Burden: The effect of tumor burden on bevacizumab clearance was also evaluated. Tumor burden was defined as the sum of the areas of all measurable lesions (cm^2). Clearance was faster in subjects with a tumor burden above the median (25.28 cm^2); mean clearance values were 3.30±1.52 and 2.47±0.85 mL/kg/day for subjects with tumor burden above and below the median, respectively ($p<0.02$). No relationship was found between volume of distribution and tumor burden.

ECOG Status: Bevacizumab clearance was lower in subjects with an ECOG status of 0 ($p<0.01$), with mean values of 2.43±1.11 and 3.35±1.29 mL/kg/day for subjects with an ECOG status of 0 and ≥1, respectively.

Serum Albumin: When pharmacokinetic parameters were compared between subjects with a serum albumin concentration above and below the median of 3.5 g/dL (the lower limit of the normal range [3.5–5.0 g/dL]), clearance was higher in subjects with baseline serum albumin levels of <3.5 g/dL ($p<0.01$) compared with a baseline albumin concentration of ≥3.5 g/dL, with mean values of 3.31±1.31 and 2.35±1.02 mL/kg/day, respectively. Baseline albumin levels below the normal range (3.5–5.0 g/dL) are known to be a predictor of poor outcome in NSCLC patients (Martin et al. 1999). Thus, the link between bevacizumab clearance and baseline albumin levels suggests a potential link between bevacizumab clearance and baseline health status.

Immunogenicity *(from Avastin labeling)*: As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin,

primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

Infusion Reactions *(from Avastin labeling)*: In clinical studies, infusion reactions with the first dose of Avastin were uncommon (<3%) and severe reactions occurred in 0.2% of patients. Infusion reactions reported in the clinical trials and postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Adequate information on rechallenge is not available. Avastin infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered. There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Avastin after experiencing a severe infusion reaction.

Surgery *(from Avastin labeling)*: Avastin therapy should not be initiated for at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of Avastin. Because of the potential for impaired wound healing, Avastin should be suspended prior to elective surgery. The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days and the interval chosen should take into consideration the half-life of the drug.

Cardiovascular Disease *(from Avastin labeling)*: Patients were excluded from participation in Avastin clinical trials if, in the previous year, they had experienced clinically significant cardiovascular disease. In an exploratory analysis pooling the data from five randomized, placebo-controlled, clinical trials conducted in patients without a recent history of clinically significant cardiovascular disease, the overall incidence of arterial thromboembolic events, the incidence of fatal arterial thromboembolic events, and the incidence of cardiovascular thromboembolic events were increased in patients receiving Avastin plus chemotherapy as compared to chemotherapy alone.

Laboratory Tests *(from Avastin labeling)*: Blood pressure monitoring should be conducted every two to three weeks during treatment with Avastin. Patients who develop hypertension on Avastin may require blood pressure monitoring at more frequent intervals. Patients with Avastin-induced or -exacerbated hypertension who discontinue Avastin should continue to have their blood pressure monitored at regular intervals. Patients receiving Avastin should be monitored for the development or worsening of proteinuria with serial urinalyses. Patients with a 2+or greater urine dipstick reading should undergo further assessment, e.g., a 24-hour urine collection.

4.4 Extrinsic Factors

1. ***What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?***

Except for combination drug administration, other factors have not been studied.

2. ***Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.***

None.

3. Drug-Drug interactions

a) Is there an in vitro basis to suspect in vivo drug-drug interaction?

No.

b) Is the drug a substrate of CYP enzymes?

No.

c) Is the drug an inhibitor and/or an inducer of CYP enzymes?

No.

d) Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No.

e) Are there other metabolic/transporter pathways that may be important?

No studies on the metabolism of bevacizumab have been performed in humans or in animals. Metabolism studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that are then recycled into other proteins. Several pathways have been described that may contribute to antibody metabolism, all of which involve biodegradation of the antibody to smaller molecules, i.e., small peptides or amino acids. This fact has been recognized in ICH Topic S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), where it is stated, "the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids" and that therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No *in vitro* drug-drug interaction studies have been performed since P_{450} enzyme system is not expected to play any role in cetuximab biotransformation.

f) Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?

No formal drug interaction studies with anti-neoplastic agents have been conducted. In Study 1, patients with colorectal cancer were given irinotecan/5-FU/leucovorin (bolus-IFL) with or without Avastin. Irinotecan concentrations were similar in patients receiving bolus-IFL alone and in combination with Avastin. The concentrations of SN38, the active metabolite of irinotecan, were on average 33% higher in patients receiving bolus-IFL in combination with Avastin when compared with bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus Avastin had a higher incidence of Grade 3–4 diarrhea and neutropenia. Due to high inter-patient variability and limited sampling, the extent of the increase in SN38 levels in patients receiving concurrent irinotecan and Avastin is uncertain (from Avastin labeling).

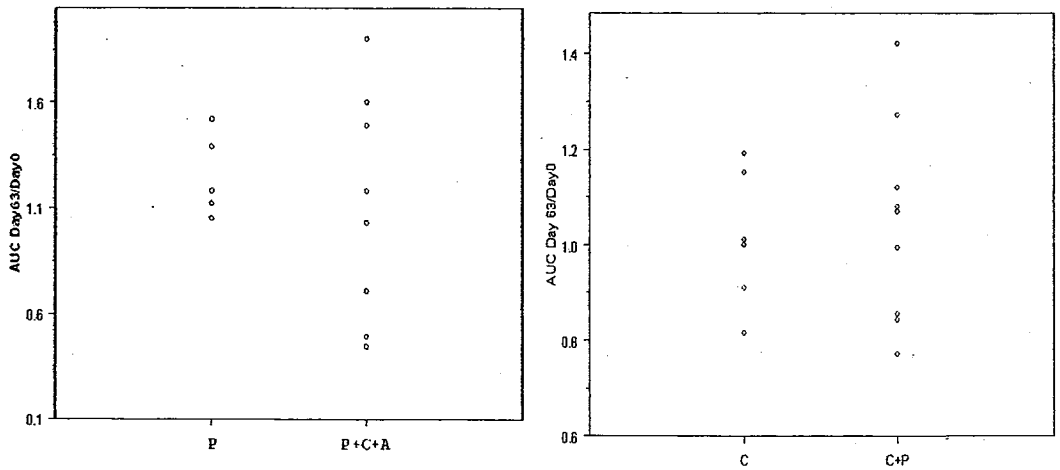
In Study AVF0757g, patients with locally advanced or metastatic (stage IIIB or IV) non-small cell lung cancer were given Avastin combined with paclitaxel/carboplatin chemotherapy. In the control arm, plasma concentration data from both Day 0 and Day 63 were available for 6 subjects for paclitaxel and 6 subjects for carboplatin. In the 15 mg/kg arm, data were available for 8 subjects for paclitaxel and 9 subjects for carboplatin. Table 14 describes the ratio of AUC_{0-180} min from Cycles 1 to 4 and individual data were plotted in Figure 7.

Table 14
Ratio of Chemotherapy Exposure after Four Cycles of Carboplatin and Paclitaxel

Arm	Carboplatin	Paclitaxel
Control		
n	6	6
Mean	1.012±0.142	1.24±0.178
Range	(0.814–1.19)	(1.05–1.52)
15 mg/kg		
n	9	8
Mean	1.047±0.210	1.105±0.537
Range	(0.771–1.42)	(0.440–1.90)

Note: Data are presented as mean ± standard deviation (range).

Figure 7. Individual AUC_{Day63}/AUC_{Day0} Value (left one for Paclitaxel and right one for Carboplatin)



Based on the data from limited number of patients with limited concentration timepoints, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin treatment had paclitaxel exposure substantially lower after four cycles of treatment (at day 63) than those at day 0 (AUC_{day63}/AUC_{day0}: 0.44, 0.49 and 0.71, respectively), while patients receiving paclitaxel/carboplatin without Avastin treatment all had greater paclitaxel exposure at day 63 than those at day 0.

g) Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

None.

h) ***Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?***

None.

i) ***Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?***

None.

4.5 General Biopharmaceutics

1. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Not applicable since this is an efficacy supplement application with a new indication and there is no manufacturing changes at this time.

4.6 Analytical

1. ***How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?***

Serum Bevacizumab concentrations were measured using an enzyme-linked immunosorbent assay (ELISA), utilizing truncated rhVEGF and a goat antibody to human IgG conjugated to horseradish peroxidase for detection. Limit of detection was 78 ng/mL. Serum VEGF concentrations were measured by an ELISA using the 3.5F8 antibody (lower limit of detection = 20 pg/mL).

2. Which metabolites have been selected for analysis and why?

None, because bevacizumab is a protein (monoclonal antibody).

3. ***For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?***

Bevacizumab serum concentrations were determined using an ELISA assay that measures total serum bevacizumab concentrations (i.e., the assay does not distinguish between bevacizumab and bevacizumab bound to VEGF ligand).

5. Labeling Recommendation

The following statement is recommended to be included in the labeling:

In Study 6 (AF0757g), based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with AVASTIN. However, 3 of the 8 patients receiving AVASTIN plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.

Hong Zhao 10/4/06

Hong Zhao, Ph.D.
Clinical Pharmacology Reviewer

Atiqur Rahman 10/05/06

Nam Atiqur Rahman, Ph.D.
Division Director, Clinical Pharmacology Division 5

6. Labeling

See separate file

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125085/85

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

Application Information			
BLA # 125085 NDA #	BLA STN# 125085/85 NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Avastin Established Name: Bevacizumab Dosage Form: 100 mg & 400 mg		Applicant: Genentech, Inc.	
RPM: Sharon Sickafuse		HFD-	Phone # 301-796-2320

NDAs only:	505(b)(2) NDAs only:
Application Type: ☐ 505(b)(1) ☐ 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (optional)	October 11, 2006
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☐ Standard X Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes **X** No
• This application is on the AIP	☐ Yes **X** No
• Exception for review *(file Center Director's memo in Administrative Documents section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in Administrative Documents section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action	**X** Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None **X** FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As X Other ASCO burst

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in Administrative Documents section)*	☐ Included
• Is approval of this application blocked by any type of exclusivity?	☐ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application?	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of	☐ Yes ☐ No

this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	10-11-06
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	10-11-06
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (full color carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	N/A
• Labeling reviews that address only carton and container labels	N/A
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☐ DMETS ☐ DSRCS X DDMAC 10-3-06 ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting/ADRA) *(indicate date of each review)*	6-1-06
❖ NDA approvals only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page	included
Debarment certification (original applications only): verified that qualifying language was not used in certification & certifications from foreign applicants are cosigned by US agent. *(Include certification.)*	X Verified

❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	10-11-06 (final version)
• Incoming submission documenting commitment	10-11-06
❖ Outgoing correspondence (letters, emails, faxes, telecons)	PMC request email 10-6-06 PMC request email 10-5-06 PMC request email 9-27-06 IR email 9-25-06 Revised PI 9-22-06 IR email 9-14-06 IR email 8-24-06 IR email 8-18-06 IR email 8-1-06 IR email 7-31-06 Filing & DI letter 6-9-06 IR fax 5-30-06 STN Assignment 4-28-06
❖ Internal memoranda, telecons, email, etc.	Mid-Cycle Meeting 8-24-06 Revised Review Committee Assignment memo 8-24-06 Revised Review Committee Assignment memo 5-9-06 Review Committee Assignment memo 5-2-06 Priority Review 4-20-06
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	
• EOP2 meeting *(indicate date)*	7-21-05, 9-2-04
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	
❖ BLAs: Product subject to lot release (APs only)?	☐ Yes X No
❖ Environmental Assessment (original and supplemental applications) (check one)	
• X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9-28-06
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (validation of sterilization & product sterility) *(indicate date of each review)*	☐ Not a parenteral product
NDAs: Facilities inspection (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation	☐ Completed

❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date, must be completed within 60 days prior to AP)*	 X Requested 9-25-06 X Accepted 9-28-06 ☐ Hold ☐ Cleared from hold

Nonclinical Information	
Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ ECAC/CAC report/memo of meeting	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	10-11-06
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	in clinical review
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	Medical imaging 8-8-06
❖ Microbiology (efficacy) review(s) *(indicate date of each review)*	X Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	in clinical review
❖ Risk Management Plan review(s) (including ODS) *(indicate location/date if incorporated into another review)*	X None
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	X Not needed
❖ Clinical Inspection Review Summary (DSI)	X None requested
• Clinical studies *(include copies of DSI letters to investigators)*	
• Bioequivalence studies *(include copies of DSI letters to investigators)*	
❖ Statistical review(s) *(indicate date of each review)*	☐ None 9-25-06
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10-5-06

LICENSING ACTION RECOMMENDATION

Applicant: Genentech, Incorporated **STN:** 125085/85

Product:

Bevacizumab

Indication / manufacturer's change:

First-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel.

■ Approval:
- ☐ Summary Basis For Approval (SBA) included
- ☐ Memo of SBA equivalent reviews included
- ☐ Refusal to File: Memo included
- ☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

☐ Inspection of establishment ☐ Inspection report included

☐ BiMo inspections completed ☐ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

■ Review of Environmental Assessment ☐ FONSI included ■ Categorical Exclusion

■ Review of labeling Date completed 10-11-06 ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

■ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: _____ Date: 10-11-06

Product Office's Responsible Division Director(s)*:

Patricia Keegan Date: 10-11-2006

_____ Date: _____

DMPQ Division Director* : _____ Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

■ Compliance status checked ■ Acceptable ☐ Hold Date: 9-28-06

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) Sharon Sickafuse Date: 10-11-06

Responsible Division Director Patricia Keegan Date: 10-11-2006
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

40 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

**Division of Drug Marketing,
Advertising, and Communications**

Internal Consult

****Pre-decisional Agency Information****

To: Sharon Sickafuse, Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D. CB 10/3/06
Division of Drug Marketing, Advertising and Communications, CDER

Date: October 3, 2006

Re: **Avastin (Bevacizumab)**
STN BL 125085/85
Comments on draft labeling

In response to your April 17, 2006, request for consultation, DDMAC has reviewed Genentech, Inc.'s proposed labeling (PI) for Bevacizumab and offers the following comments. Comments are provided for the revised PI provided by electronic mail on October 2, 2006.

Genentech has submitted a sBLA for a new indication for the use of Bevacizumab as first-line treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer in combination with platinum-based chemotherapy.

Line #	Current PI Statement	Comment
220 - 221	[redacted]	[redacted]

b(4)

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drugs Evaluation & Research - Food & Drug Administration
Division of Monoclonal Antibodies
NIH Campus, Building 29B, Room 3NN18, HFD-123
10903 New Hampshire Ave, Silver Spring, MD 20993
Telephone (301) 827-0850
Facsimile (301) 827-0852

Date: September 28, 2006
From: Patrick Swann, Ph.D.
Subject: BLA 125085.85: Categorical Exclusion for Environmental Assessment
Through: Kathleen A. Clouse, Ph.D. Acting Director, DMA
To: Sharon Sickafuse
BLA 125085.85 File

Sponsor: Genentech
License Number: 1048

Background:
The sponsor states that this Biologics License Application qualifies for a categorical exclusion from the Environmental Assessment (EA) requirement. Specifically under 21 CFR Section 25.31(c), any action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, is categorically excluded and ordinarily does not require the preparation of an EA or an Environmental Impact Statement for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Sponsor states that, to its knowledge, no extraordinary circumstances exist.

The claim of categorical exclusion is accepted.

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Monday, September 25, 2006 3:30 PM
To: CDER-TB-EER
Subject: Request for compliance check for Bevacizumab PAS [STN 125085/85]

Importance: High

STNs: 125085/85

Product: Bevacizumab (Avastin)

Company: Genentech, Inc.

License #: 1048

Drug Substance manufactured at the following 3 facilities:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
Registration no: 2917293/SAN

Genentech, Vacaville
000 New Horizons Way
Vacaville, CA 95688
Registration no: 2954595

Genentech Espana
Aptdo.De Correos #85
La Relba, s/n
36410 Porrino (Pontevedre)
Spain
Registration no: 3003134808

Drug Product is manufactured at the South San Francisco facility.

The action due date is October 11th.

Thank you

Sickafuse, Sharon

From: Merritt, Babette A
nt: Thursday, September 28, 2006 12:35 PM
: Sickafuse, Sharon
Cc: Hoyt, Colleen; Harper Velazquez, Tia M
Subject: RE: Request for compliance check for Bevacizumab PAS [STN 125085/85]

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the compliance check request below. There are no pending or ongoing compliance actions to prevent approval of STN 125085/85 at this time.

The following is the current status:

Manufacturer	*FEI #*	*Date Last EI*	*Profile*	*Status*
Genentech NAI 5/06	*2917293*	*3/9/06*	*CBI, SVS, TRP*	*AC*
Genentech NAI 5/04	*2954595*	*2/13/04*	*CBI*	*AC*

***Genentch Espana --- no listing on this --- will check with our Foreign group.*

ave a good day,
abette

Babette Angela Merritt
Consumer Safety Officer
Office of Compliance, CDER, HFD-323
Food and Drug Administration

From: Sickafuse, Sharon
Sent: Monday, September 25, 2006 3:30 PM
To: CDER-TB-EER
Subject: Request for compliance check for Bevacizumab PAS [STN 125085/85]
Importance: High

STNs: 125085/85

Product: Bevacizumab (Avastin)

Company: Genentech, Inc.

License #: 1048

Drug Substance manufactured at the following 3 facilities:

Genentech, Inc.

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Registration no: 2954595

Genentech Espana
Aptdo.De Correos #85
La Relba, s/n
36410 Porrino (Pontevedre)
Spain
Registration no: 3003134808

Drug Product is manufactured at the South San Francisco facility.

The action due date is October 11th.

Thank you

Sickafuse, Sharon

From: Merritt, Babette A
Sent: Thursday, September 28, 2006 2:18 PM
To: Sickafuse, Sharon
Cc: Hoyt, Colleen; Harper Velazquez, Tia M
Subject: Compliance Check for STN 125085/85

I checked with our Foreign Inspection Team regarding Genentech Espana and the following is the current status:

FEI # 3003134808 Last Inspection: 9/22/05 Status: Acceptable Classif.: 10/05 VAI

Have a good day,
Babette

Babette Angela Merritt
Consumer Safety Officer
Office of Compliance, CDER, HFD-323
Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 24, 2006 SKS

From: Sharon Sickafuse, OODP/DBOP

To: STN 125085/85
Bevacizumab

Subject: Mid-Cycle Review Meeting

PARTICIPANTS:

CDER/OODP:	Joe Gootenberg, Karen Jones, Pat Keegan, Lydia Martynec, Lee Pai-Scherf, Jeff Summers,
CDER/OB:	Yuan-Li Shen, Mark Rothmann
CDER/OCP:	Hong Zhao

The mid-cycle review meeting was held on August 24, 2006, to discuss the status of the reviews for the Genentech Bevacizumab priority sBLA 125085/85 that provides for a new indication, first-line treatment of patients with locally advanced, metastatic, or recurrent non-small cell lung cancer in combination with platinum-based chemotherapy.

Dr. Jeff Summers gave a presentation supplement and the status of his review. Drs. Yuan-Li Shen and Hong Zhao also gave presentations of their reviews.

BLA/NDA/PMA
Review Committee Assignment Memorandum

☐ Initial Assignment
☒ Change

STN: 125085/85

Applicant: Genentech, Inc.

Product: Bevacizumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
	Reg. Project Manager	Admin/Regulatory		
	Reviewer	Admin/Regulatory		
		Product*		
	Reviewer	Product*		
	Reviewer	Product		
		Clinical		
	Reviewer	Clinical		
Hong Zhao	Reviewer	Clinical Pharmacology	H. Zhao	8-18-06
	Reviewer	Pharm/Tox		
	Reviewer	Biostatistics		
	Reviewer	BiMo		
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
	Reviewer	Labeling		
		Other		

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
I. Mahmood	Reviewer	Clinical Pharmacology	Hong Zhao	8-18-06

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Sharon Slickafuse — Name Printed / Signature

8-24-06 — Date

Memo entered in RMS by: _____ Date: 9/1/06 QC by: _____ Date: _____

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125085/85 Product: Bevacizumab Applicant: Genentech

Final Review Designation (circle one): Standard (Priority)

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 6-1-06 Committee Recommendation (circle one): (File) RTF

RPM: Sickafuse 6-1-06
(signature/date)

Attachments:

- [X] Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - [X] Part A – RPM
  - [ ] Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - [ ] Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - [X] Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Summers _____ Shen _____ _____
- [ ] Memo of Filing Meeting

STN 125085/85 Product Bevacizumab Part A Page 1

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?		Brief justification, action & status
Cover Letter	(Y)	N	
Form 356h completed	(Y)	N	
▫ including list of all establishment sites and their registration numbers	(Y)	N	
▫ If foreign applicant, US Agent signature.	Y	N	
Comprehensive Table of Contents	(Y)	N	
Debarment Certification with correct wording (see * below)	(Y)	N	
User Fee Cover Sheet	(Y)	N	
User Fee payment received	(Y)	N	
Financial certification &/or disclosure information	(Y)	N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	(Y)	N	
Pediatric rule: study, waiver, or deferral	(Y)	N	
Labeling:	(Y)	N	
▫ PI –non-annotated	(Y)	N	
▫ PI –annotated	(Y)	N	
▫ PI (electronic)	(Y)	N	
▫ Medication Guide	Y	N	
▫ Patient Insert	Y	N	
▫ package and container	Y	N	
▫ diluent	Y	N	
▫ other components	Y	N	
▫ established name (e.g. USAN)	Y	N	
▫ proprietary name (for review)	Y	N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?		Brief justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y)	N	
▫ legible	(Y)	N	
▫ English (or translated into English)	(Y)	N	
▫ compatible file formats	(Y)	N	
▫ navigable hyper-links	(Y)	N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y)	N	
▫ summary reports reference the location of individual data and records	(Y)	N	

125085/85

STN ~~10370~~ Product Bwaciumab Part A Page 2

Examples of Filing Issues	Yes?	Brief justification, action, & status
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement:		
☐ description and results of studies performed to evaluate the change	Y N	
☐ relevant validation protocols	Y N	
☐ list of relevant SOPs	Y N	
if clinical supplement:		
☐ changes in labeling clearly highlighted	(Y) N	
☐ data to support all label changes	(Y) N	
☐ all required electronic components, including electronic datasets (e.g. SAS)	(Y) N	
if electronic submission:		
☐ required paper documents (e.g. forms and certifications) submitted	(Y) N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? no

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: _____
- Dates: _____

Recommendation (circle one): (File) RTF

RPM Signature: Sharon Sickafuse Branch Chief concurrence: Karen D Jones

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
◻ Biopharmaceutics and associated analytical methods	Y	(N)	not required
◻ Clinical pharmacology [includes immunogenicity]	Y	(N)	not required
◻ Clinical Efficacy [for each indication]	(Y)	N	
◻ Clinical Safety	(Y)	N	
◻ Synopses of individual studies	(Y)	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	
Study Reports and related information [5.3]	Y	N	
◻ Biopharmaceutic	Y	(N)	not required
◻ Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y)	N	
◻ Pharmacokinetics (PK)	(Y)	N	
◻ Pharmacodynamic (PD)	(Y)	N	
◻ Efficacy and Safety	(Y)	N	
◻ Postmarketing experience	(Y)	N	
◻ Case report forms	(Y)	N	
◻ Individual patient listings (indexed by study)	(Y)	N	
o electronic datasets (e.g. SAS)	(Y)	N	
Literature references and copies [5.4]	(Y)	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
◻ legible	(Y)	N	
◻ English (or certified translation into English)	(Y)	N	
◻ compatible file formats	(Y)	N	
◻ navigable hyper-links	(Y)	N	
◻ interpretable data tabulations (line listings) & graphical displays	(Y)	N	

Examples of Filing Issues	Yes?	If not, action & status
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	(Y) N	
☐ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y (N)	not required
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y (N)	not required
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	(Y) N	not required during IND review
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y (N)	not required
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y (N)	not required no AIs have occurred
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	not required
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electronic datasets complete & usable?	Bridge status identified?
E4599	(Y) N	(Y) N NR	(Y) N	Y N (NR)
0757g	(Y) N	(Y) N NR	(Y) N	Y N (NR)
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

none

Is clinical site(s) inspection (BiMo) needed?

no

Is an Advisory Committee needed?

no

Recommendation (circle one): File RTF

Reviewer: 6/6/06 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: 6/6/06 Division. Director: P. Keegan 6-6-2006
(signature/ date) (signature/ date)

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

none

Is clinical site(s) inspection (BiMo) needed?

NO

Is an Advisory Committee needed?

NO

Recommendation (circle one): File RTF

Reviewer: V Summers 06/06/06 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [signature] 6/06/06
(signature/ date)

Division. Director: V Summers 06/06/06 for Pat Keegan Division Director
(signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
☐ Biopharmaceutics and associated analytical methods	Y N	NA
☐ Clinical pharmacology [includes immunogenicity]	Y N	NA
☐ Clinical Efficacy [for each indication]	(Y) N	
☐ Clinical Safety	(Y) N	
☐ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	Y N	
☐ Biopharmaceutic	Y N	NA
☐ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	NA
☐ Pharmacokinetics (PK)	Y N	NA
☐ Pharmacodynamic (PD)	Y N	NA
☐ Efficacy and Safety	(Y) N	
☐ Postmarketing experience	Y N	NA
☐ Case report forms	(Y) N	
☐ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
☐ legible	(Y) N	
☐ English (or certified translation into English)	(Y) N	
☐ compatible file formats	(Y) N	
☐ navigable hyper-links	(Y) N	
☐ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes*	If not, action & status
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	Y N	NA
☐ conducted in compliance with requirements for informed consent	Y N	NA
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y (N)	Not required
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	NA
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

STN 125085 Product Bevacizumab

Examples of Filing Issues	Yes		If not, action & status
data supporting the proposed dose and dose interval	Y	N	NA
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y)	N	
adequate characterization of product specificity or mode of action	Y	N	NA
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	N	NA
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	N	NA
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BMF sites identified?			
E4599	(Y)	N	Y	N	NR NA	(Y)	N	Y	N	NR	NA
	Y	N	Y	N	NR	Y	N	Y	N	NR	
	Y	N	Y	N	NR	Y	N	Y	N	NR	
	Y	N	Y	N	NR	Y	N	Y	N	NR	
	Y	N	Y	N	NR	Y	N	Y	N	NR	
	Y	N	Y	N	NR	Y	N	Y	N	NR	
	Y	N	Y	N	NR	Y	N	Y	N	NR	
	Y	N	Y	N	NR	Y	N	Y	N	NR	
	Y	N	Y	N	NR	Y	N	Y	N	NR	
	Y	N	Y	N	NR	Y	N	Y	N	NR	

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): File RTF

Reviewer: [signature] 6/1/06 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: _____ Division. Director: Alaka Chakravarty
(signature/ date) (signature/ date)

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : STN 125085/85 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A

FDA Received Date: 4-11-06 **Action Date:** 10-11-06

HFM _____ **Product and Proprietary names/dosage form:** Bevacizumab (Avastin) solution for injection
(IV)

Applicant: Genentech, Inc. **Therapeutic Class:** N/A

Indication(s) previously approved:
First-line and second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: First-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous non-small cell lung cancer in combination with carboplatin and paclitaxel.

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ☐ **Partial Waiver** ☐ **Deferred** ☐ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☑ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:

Sharon Sickafuse
_____
Regulatory Project Manager

cc: NDA/BLA #
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03;revised 8-10-04 for RMS/BLA use)

Debarment Certification

The National Cancer Institute (NCI) hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with study E4599 that investigated the product bevacizumab.

Signed by: _____ 26 July 2005

Sherry Ansher, Ph.D. Date
Coordinator
Research and Development Agreements
Regulatory Affairs Branch
CTEP, NCI

Genentech
IN BUSINESS FOR LIFE

DEPARTMENT OF REGULATORY AFFAIRS

1 DNA Way MS#242
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

October 11, 2006

Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **License No. 1048**
STN: BL 125085/85.020
AVASTIN® (bevacizumab)
Amendment to a Pending Application
Postmarketing Commitments Proposal for E4599 sBLA

Dear Dr. Keegan:

We refer to Genentech's Biologics Application (BLA) for AVASTIN® (bevacizumab) in combination with intravenous 5-fluorouracil-based chemotherapy for the first line treatment of patients with metastatic carcinoma of the colon or rectum, approved on 26 February 2004. Reference is also made to Genentech's pending BLA supplement for the addition of Avastin for use in combination with platinum-based chemotherapy for the first-line treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer other than predominant squamous histology (STN: BL 125085/85).

The purpose of this submission is to provide the final post-marketing commitments (PMC) proposal based on agreements reached in e-mail communications between the FDA and Ms. Brisdell Hunte on 11 October 2006.

This submission is being submitted via secure e-mail. Symantec Norton Antivirus Corporate Edition (Program version 9.0.2.1000, with the most recent Virus Definition File version) was used to ensure the file is virus-free.

If you have any questions regarding this submission, please contact Brisdell Hunte, Manager, Regulatory Affairs at (650) 225-6829.

Sincerely,
Todd W. Rich, M.D.
Vice President
Clinical and Commercial Regulatory Affairs

Avastin-2386 sub mg

125085/85
FDA Final PMCs
10/11/06

1. To submit an efficacy supplement containing the final study report, including summary analyses, primary datasets and appropriate revised labeling describing the effects of overall survival in the entire population and by gender and age, from the Hoffman-LaRoche-sponsored study, BO17704, "A Randomized, Double-Blind, Multicenter Phase 3 Study of Bevacizumab in Combination with Cisplatin and Gemcitabine Versus Placebo, Cisplatin and Gemcitabine in Patients with Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer Who Have Not Received Prior Chemotherapy". A copy of the protocol was submitted to BB-IND 7023 on February 13, 2006 and patient accrual was completed by August 31, 2006. The study will be completed by June 20, 2008, and the supplement containing the final study report and revised labeling will be submitted by December 31, 2008.

2. To submit as a supplement a final safety report, and revised labeling, describing the adverse event profile of Avastin administered to patients with previously treated central nervous system (CNS) metastases. The supplement will contain information on an integrated safety population of at least 50 patients with previously treated CNS metastases enrolled on studies AVF3752g or AVF3671g, to include summary safety analyses, primary datasets with demographic, treatment and safety information, case report forms for all deaths and dropouts, and narrative summaries for all patients in the integrated safety population with serious adverse events in either study. For those patients enrolled in Study AVF3752g, the supplement will contain information on the number and size of brain metastases. Protocol AVF3752g was submitted to BB-IND 7023 on November 30, 2005. Protocol AVF3671g will be submitted to BB-IND 7023 by November 30, 2006, accrual of the minimum number of 50 patients will occur by January 31, 2008 and the supplement containing the final safety report and revised labeling will be submitted by March 31, 2008.

3. To submit a safety update on an annual basis containing safety information summarizing and characterizing NCI CTC ver. 3 Grade 2-5 adverse events involving the CNS from the following three placebo-controlled, randomized studies: OSI3364g (non-small cell lung cancer) and AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). For studies which have not been completed, the annual update of information will be generated by an independent unblinded data coordinating center that will not share information with any individual involved in the design, conduct or analysis of the trials. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005 and protocol AVF3693g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 30, 2006, and the annual safety updates will be submitted by Dec. 31, 2007, Dec. 31, 2008, and Dec, 31, 2009.

4. To submit as a supplement a final safety report containing revised labeling, as applicable, based on data from a minimum of 100 patients with CNS metastases (roughly half of whom were randomized to Bevacizumab plus additional anti-cancer agents) enrolled in studies OSI3364g (non-small cell lung cancer), AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). The supplement will include summary analyses and primary datasets, including the number and size of CNS metastases for each patient. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005 and protocol AVF3693g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 30, 2006, a statistical analysis plan for integrated summary analyses will be submitted by June 30, 2007, and the supplement containing the final safety report and revised labeling will be submitted by December 31, 2010.

5. To conduct a sub-study to address the impact of Bevacizumab on the QT interval. This sub-study will be added to three planned or ongoing randomized placebo-controlled studies in breast cancer, ovarian cancer, and extensive stage small cell lung cancer. The sub-study will collect replicate ECG measurements at baseline and at various time points correlating with drug exposure. Approximately 60 Bevacizumab-treated patients and 60 controls will be evaluated in this sub-study. A detailed protocol for this sub-study will be submitted by January 31, 2007. The sub-study will be initiated by June 30, 2007 and will be completed by June 30, 2010. A report based on this study will be submitted by December 31, 2010.

Sickafuse, Sharon

From: Gootenberg, Joseph
Sent: Wednesday, October 11, 2006 2:46 PM
To: 'hunte@gene.com'
Cc: Sickafuse, Sharon; Summers, Jeff; Lee, Cathryn; Keegan, Patricia
Subject: RE: 125085/85 Revised Draft PMCs
Attachments: 125085.85 FDA Draft PMCs 10.11.06 clean.doc

Brisdell,
Per our telephone conversation, PMCs attached.
Thanks,
Joe

125085/85
FDA Draft PMCs
10/11/06

1. To submit an efficacy supplement containing the final study report, including summary analyses, primary datasets and appropriate revised labeling describing the effects of overall survival in the entire population and by gender and age, from the Hoffman-LaRoche-sponsored study, BO17704, "A Randomized, Double-Blind, Multicenter Phase 3 Study of Bevacizumab in Combination with Cisplatin and Gemcitabine Versus Placebo, Cisplatin and Gemcitabine in Patients with Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer Who Have Not Received Prior Chemotherapy". A copy of the protocol was submitted to BB-IND 7023 on February 13, 2006 and patient accrual was completed by August 31, 2006. The study will be completed by June 20, 2008, and the supplement containing the final study report and revised labeling will be submitted by December 31, 2008.

2. To submit as a supplement a final safety report, and revised labeling, describing the adverse event profile of Avastin administered to patients with previously treated central nervous system (CNS) metastases. The supplement will contain information on an integrated safety population of at least 50 patients with previously treated CNS metastases enrolled on studies AVF3752g or AVF3671g, to include summary safety analyses, primary datasets with demographic, treatment and safety information, case report forms for all deaths and dropouts, and narrative summaries for all patients with serious adverse events in either study. For those patients enrolled in Study AVF3752g, the supplement will contain information on the number and size of brain metastases. Protocol AVF3752g was submitted to BB-IND 7023 on November 30, 2005. Protocol AVF3671g will be submitted by November 30, 2006, accrual of the minimum number of 50 patients will occur by January 31, 2008 and the supplement containing the final safety report and revised labeling will be submitted by March 31, 2008.

3. To submit a safety update on an annual basis containing safety information summarizing and characterizing NCI CTC ver. 3 Grade 2-5 adverse events involving the CNS from the following three placebo-controlled, randomized studies: OSI3364g (non-small cell lung cancer) and AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). For studies which have not been completed, the annual update of information will be generated by an independent unblinded data coordinating center that will not share information with any individual involved in the design, conduct or analysis of the trials. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005 and protocol AVF3995g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 30, 2006, and the annual safety updates will be submitted by Dec. 31, 2007, Dec. 31, 2008, and Dec, 31, 2009.

4. To submit as a supplement a final safety report containing revised labeling, as applicable, based on data from a minimum of 100 patients with CNS metastases (roughly half of whom were randomized to Bevacizumab plus additional anti-cancer agents) enrolled in studies OSI3364g (non-small cell lung cancer), AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). The supplement will include summary analyses and primary datasets, including the number and size of CNS metastases for each patient. Protocol OSI3364 was submitted to BB-IND 7023 on April 27, 2005 and protocol AVF3993g was submitted to BB-IND 7023 on November 22, 2005. Protocol AVF3995g will be submitted by November 20, 2006, a statistical analysis plan for integrated summary analyses will be submitted by June 30, 2007, and the supplement containing the final safety report and revised labeling will be submitted by December 31, 2010.

5. To conduct a sub-study to address the impact of Bevacizumab on the QT interval. This sub-study will be added to three planned or ongoing randomized placebo-controlled studies in breast cancer, ovarian cancer, and extensive stage small cell lung cancer. The sub-study will collect replicate ECG measurements at baseline and at various time points correlating with drug exposure. Approximately 60 Bevacizumab-treated patients and 60 controls will be evaluated in this sub-study. A detailed protocol for this sub-study will be submitted by January 31, 2007. The sub-study will be initiated by June 30, 2007 and will be completed by June 30, 2010. A report based on this study will be submitted by December 31, 2010.

Sickafuse, Sharon

: Gootenberg, Joseph
Sent: Friday, October 06, 2006 5:51 PM
To: 'hunte@gene.com'
Cc: Summers, Jeff; Keegan, Patricia; Jones, Karen; Sickafuse, Sharon; Lee, Cathryn
Subject: RE: 125085/85 Revised Draft PMCs
Attachments: 125085-85 PMC FDA DRAFT revised 100606 PM clean.doc

Brisdell,
I'm sorry, but after conferring with our PMC expert, we have decided to split PMC 1, which contains two separate deliverables, into two separate PMCs.
Please work from the attached revised PMCs, They also contain some edits for clarity and grammar.
Thanks,
Joe

From: Gootenberg, Joseph
Sent: Friday, October 06, 2006 4:55 PM
To: 'hunte@gene.com'
Cc: Summers, Jeff; Keegan, Patricia; Jones, Karen; Sickafuse, Sharon; Lee, Cathryn
Subject: 125085/85 Draft PMCs

Brisdell,
Attached please find Draft PMCs as discussed today.
Thanks,
Jo

From: Brisdell Hunte [mailto:hunte.brisdell@gene.com]
Sent: Friday, October 06, 2006 4:46 PM
To: Gootenberg, Joseph
Cc: Summers, Jeff; hunte@gene.com
Subject: RE: CALL FDA 301 796-1362 immediately

Hi again, we would like to propose submission of the analysis plan for pooled randomized information for patients with CNS metastases by June 2007. Would that be acceptable? Regards, Brisdell

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Request for Post-Marketing Commitments for STN 125085/85

1. If the Hoffman-LaRoche-sponsored study, BO17704 demonstrates improved progression free survival, Genentech will submit an efficacy supplement containing appropriate revised labeling by March 2008.

2. Genentech will submit an efficacy supplement containing overall survival results from the Hoffman-LaRoche-sponsored study, BO17704 and appropriate revised labeling by December 2008.

3. Genentech will submit by March 2008 a safety supplement containing an analysis of pooled non-randomized data from at least 50 patients enrolled on studies AVF3752g and AVF3671g. This supplement will contain revised labeling on the safety of Avastin use in patients with previously treated CNS metastases. Information on the number and size of brain metastases for patients enrolled on Study AVF3752g will be included in this supplement.

4. Genentech will submit on an annual basis for 4 years beginning in December 2007 safety information for all Grade 2 or greater CNS-related adverse events from three placebo-controlled, randomized studies conducted by Genentech. These studies include on-going studies OSI3364g (non-small cell lung cancer) and AVF3693g (metastatic breast cancer) and a planned study in small cell lung cancer, AVF3995g. The annual update of information for each study prior to completion will be provided to the FDA through an independent data monitoring committee in an unblinded fashion.

5. Genentech will submit a safety supplement to include revised labeling based on data from approximately 100 patients with CNS metastases (roughly half of whom were randomized to Avastin plus additional anti-cancer agents) enrolled in studies OSI3364g (non-small cell lung cancer), AVF3693g (metastatic breast cancer) and AVF3995g (small cell lung cancer). Information on the number and size of brain metastases for patients enrolled on Studies AVF3752g, AVF3693g and AVF3995g will be included in this supplement. A statistical analysis plan for this combined analysis will be submitted by June 2007. The safety supplement and accompanying revised labeling will be submitted by December 2010.

6. Genentech agrees to conduct a substudy to address the impact of bevacizumab on the QT interval. This substudy will be added to 3 planned or ongoing randomized placebo-controlled studies in breast cancer, ovarian cancer, and extensive stage small cell lung cancer. The substudy will collect replicate ECG measurements at baseline and at various time points correlating with drug exposure. Approximately 60 Avastin-treated patients and 60 controls will be evaluated in this substudy. A detailed protocol for this substudy will be submitted by January 2007. The substudy will be initiated by June 2007 and will be completed by June 2010. A report based on this study will be submitted in December 2010.

Sickafuse, Sharon

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n: Sickafuse, Sharon
Sent: Thursday, October 05, 2006 1:11 PM
To: 'hunte@gene.com'
Subject: Revised PMC list for STN 125085/85
Attachments: 125085-85 PMC Sumemrs 04-OCT-06.doc

Request for Post-Marketing Commitments for STN 125085/85

1. Genentech will provide an efficacy supplement containing revised labeling for the Hoffman-LaRoche-sponsored study, BO17704 by March 2008, if the study demonstrates improved progression free survival. Regardless of a submission of an efficacy supplement based on PFS data, Genentech will provided an efficacy supplement containing overall survival results and revised labeling for the Hoffman-LaRoche-sponsored study, BO17704 by December 2008.

2. Genentech will provide a safety supplement containing an analysis of pooled non-randomized data from study AVF3752g. The safety supplement will contain revised labeling based on results from Study AVF3752g consisting of information on at least 50 patients by March 2008. In this report, information on the number and size of brain metastases for Study AVF3752g will be provided.

3. Genentech will provide pooled safety information regarding adverse events involving the CNS in patients with CNS metastases from the randomized studies OSI3364g and AVF3671g on an annual basis beginning in October 2007. A safety supplement and accompanying safety report on at least 100 patients with CNS metastases (50 patients randomized to Avastin plus additional anti-cancer agents) will be provided by [Genentech, please provide a date].

4. To conduct a study, addressing the principles discussed in the ICH-E14 guidance document, that will assess the impact of Bevacizumab on the QT interval. The study will collect replicate ECG measurements at baseline and at various timepoints correlating with drug exposure, e.g., C_{max} and steady state. The study will be submitted [GNE provide date within 3 months of approval of the NSCLC supplement]. The study will be initiated [GNE give date] study completion by [GNE give date] and final study report will be submitted [give date].

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Wednesday, September 27, 2006 2:21 PM
To: 'hunte@gene.com'
Subject: request for PMCs for STN 125085/85

Attachments: GNE PMCs.doc

GNE PMCs.doc (35 KB)

Request for Post-Marketing Commitments for STN 125085/85

1. To submit either an efficacy supplement or the final study report for the Hoffman-LaRoche-sponsored study, BO17704. An efficacy supplement containing revised labeling should be submitted if the study results do not demonstrate a survival benefit in females (hazard ratio ≥ 0.95) on the cisplatin and gemcitabine plus Bevacizumab arm compared to the cisplatin and gemcitabine alone arm or if the results provide other important information regarding efficacy or safety that should be included in product labeling..

   Genentech – please propose the PMC timelines/goals for PMC #1.

2. To conduct and submit the results of a review of all available Genentech and Roche safety databases and of literature reports characterizing the incidence and severity of adverse events involving the central nervous system reported in patients with CNS metastases receiving Avastin. The safety update will be submitted within [Date occurring within 3 months of approval of the NSCLC supplement] and shall contain revised labeling, if warranted by the data.

3. If the safety update (described above) provides insufficient data to characterize the risks of administration of Bevacizumab in patients with CNS metastases in product labeling, Genentech will submit a description of the plan, including one or more protocols, for assessment of the risks of Bevacizumab use in patients with CNS metastases arising from colorectal cancer or non-squamous non-small cell lung cancer origin. The study(ies) will be conducted in patients with CNS metastases from CRC or non-squamous NSCLC who will receive a specified chemotherapy regimen and will be randomized to receive Avastin plus chemotherapy or chemotherapy alone. Randomization should be stratified for variables that may affect risk of CNS hemorrhage, such as the number of, total volume of, and history of prior radiotherapy for of CNS metastases. The study will also incorporate a data monitoring committee to evaluate the safety of continued Bevacizumab administration in patients with CNS metastases. The protocol should be submitted to the FDA and the study initiated within 6 months of approval of the NSCLC supplement and completed by October 2008. The final study report should be submitted to FDA by February 2009.

4. To conduct a study, addressing the principles discussed in the ICH-E14 guidance document, that will assess the impact of Bevacizumab on the QT interval. The study will collect replicate ECG measurements at baseline and at various timepoints correlating with drug exposure, e.g., C_{max} and steady state. The study will be submitted [GNE provide date within 3 months of approval of the NSCLC supplement]. The study will be initiated [GNE give date] study completion by [GNE give date] and final study report will be submitted [give date].

S fuse, Sharon

From: Sickafuse, Sharon
Sent: Monday, September 25, 2006 10:56 AM
To: 'hunte@gene.com'
Subject: IR request for STN 125085/85

b(6)

'lease clarify why the List of Updated Post-March 2002 "Investigators with Disclosure" Table submitted on 15-SEP-06 depicts Drs. as having a answered "yes" to question 3 on the CTEP disclosure form but the actual disclosure forms ubmitted with the original application show that these investigators answered "yes" to question 4, an equity investment of greater ıan 50,000 dollars.

Sickafuse, Sharon

om: Sickafuse, Sharon
ent: Friday, September 22, 2006 4:50 PM
To: 'hunte@gene.com'
Subject: Bevacizumab NSCLC PI

Attachments: Revised PI_FDA 9.22.06.doc

STN 125085/85

Hi Brisdell,

As it turns out, I am able to send you this much earlier than I thought. This revision is based on Genentech's PI submission of 8-15-06. I did receive your submission of 9-15-06 containing a revised PI, but by that time, the team had already started to work on the 8-15-06 version. You will note that the AE section has been completely revised. As we discussed, when you send the PI back to me, please include the language from yesterday's CBE approval.

I have a question for you. Did Genentech trademark the name "Avastin" as Avastin or AVASTIN?

Revised PI_FDA 9.22.06.doc (5...

40 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Sickafuse, Sharon

m: Sickafuse, Sharon
nt: Thursday, September 14, 2006 5:13 PM
To: 'hunte@gene.com'
Subject: STN 125085/85 - biostatistician request

ECOG's 2nd interim analysis on overall survival was based on a total of 469 deaths with a February 9, 2005 cutoff date. Applying the Feb. 9, 2005 cutoff date with the submitted data (with Dec. 30, 2005 cut-off), there were a total of 581 deaths. Based on an analysis of this dataset that applies the February 9, 2005 cutoff date, the agency obtained a hazard ratio estimate of 0.81 with a nominal p-value of 0.012 from the stratified log rank test. For inferential purposes we believe that this is the most appropriate analysis. Please inform us whether you are in agreement with the results of this analysis.

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Thursday, August 24, 2006 4:27 PM
To: 'hunte@gene.com'
Subject: IR for STN 125085/85

Attachments: IR Genentech 4599 20-AUG-06 rev 24-AUG-06.doc

IR Genentech 4599
20-AUG-06 re...

Information Request to Genentech for E4599
STN:125085.85
24-AUG-06

1. Patient numbers 45071, 45515 and 53038 are documented in the tumor response summary CRT as having had a complete response (CR), yet there are no documented target tumor lesions or tumor measurements in the tumor assessment CRT. Please clarify if these patients were included in the ORR determinations, and if included, the rationale for this type of response being characterized as a CR.

2. Protocol E4599, Section 5.321, Proteinuria, reads as follows:

   A dipstick urinalysis is required prior to each bevacizumab infusion. Trace + proteinuria on dipstick urinalysis should not be considered a positive result, but should be repeated. If repeat confirms trace + proteinuria, no additional evaluation is necessary and the patient should continue therapy as planned. At initial documentation of significant proteinuria (> 1+ by urine dipstick), patients should undergo additional evaluation including the following:

   - 24-hour urine collection for total protein and creatinine clearance
   - Urine protein/creatinine ratio
   - Urinary protein electrophoresis
   - Microscopic examination of fresh urine

   If the 24-hour urine collection confirms proteinuria < 2000 mg within 24 hours, the patient may continue bevacizumab treatment as planned. A 24-hour urine collection for total protein and creatinine clearance must be performed prior to each subsequent cycle of therapy (every 3 weeks) to monitor the degree of proteinuria until it has decreased to < 500 mh/24 hours.

   Patients who develop > 2000 mg proteinuria within 24 hours should continue treatment with paclitaxel and carboplatin and should not receive additional doses of bevacizumab until the proteinuria improves to < 2000 mg within 24 hours. Patients can then resume treatment at the same dose and schedule. The 24-hour urine collection should be repeated at the start of each subsequent 3-week cycle of therapy to monitor the degree of proteinuria.

   The "Urine" data set provided in the submission documents 66 patients with at least one urine dipstick reading of 2^+ or greater, while only 3 of 66 patients had a 24 hour urine protein measurement recorded. Three of the patients for whom no 24 hour urine protein measurements were recorded had urine dip stick readings of 4^+. Please clarify if this lack of 24 hour urine protein data in the "Urine" data set represents a failure in -study conduct, or -recording of data. If there are additional "Internal" ECOG forms on which this data was recorded, please provide the internal forms for review. FDA notes that 27 patients had urine dipstick measurements of 2^+ or greater and were administered bevacizumab on the same date as the urine dipstick reading was performed. If the lack of 24 hour urine protein measurements is because the protocol was not adhered to, please provide a discussion regarding this failure in study conduct and how it reflects on study conduct as a whole, and most importantly, how it reflects on ECOG auditing procedures.

Sickafuse, Sharon

)m: Sickafuse, Sharon
,nt: Friday, August 18, 2006 10:09 AM
To: 'hunte@gene.com'
Subject: IR for STN 125085/85

Attachments: Bev lung IR.doc

Bev lung IR.doc (1 MB)

Information Request to Genentech for Study E4599
August 18, 2006

1. The ADV data set provided for review contains 92 adverse events classified as unmapped in the AEBCTC and AEPCTC data columns. The following 30 patients contain unmapped adverse events:

   45185, 45341, 45348, 45351, 45352, 45367, 45376, 45403, 45409, 45439, 45448, 45464, 45466, 45471, 45500, 45502, 45522, 45532, 45550, 47039, 50004, 50089, 52012, 52035, 52040, 53003, 53026, 53030, 53032, and 53036.

   The adverse events that were unmapped in the AEBCTC and AEPCTC data columns were described by the investigator in the TOXDSI data column as follows:

   AIK PHOS INCREASED, ALK PHOS, ALLERGY OTHER RASH:, ANOREXIA, ANXIETY, BLEEDING-ROSE, CARDIOVASCULAR GENERAL, CHILLS, CONSTIPATION, DEATH R/T PROGRESSIVE DISEASE, DERMATOLOGY/SKIN DERMATITIS, DRY MOUTH, EDEMA- L ANKLE, EPISTAXIS, FLATULENCE, HEMATURIA, HEMORRHOIDS, HOARSNESS, HYPERCALCEMIA, HYPERGLYCEMIA, HYPERTENSION, INCREASED BLOOD GLUCOSE, INFECTION WITHOUT NEUTROPENIA, INFECTION-THRUSH, INFECTION-UTI, L AXILLARY AREA, LDH, LE EDEMA, LIMB PAIN, LYMPHATICS, LYMPHOPENIA, MOOD ALT DEPRESSION, MUSCULOSKELETAL, NARES-DRY, NEUROPATHY, PAIN, PAIN - BACK, PAIN BACK, PAIN BONE, PAIN FROM FALL, PAIN L SHOULDER, PAIN LEFT AXILLA, PAIN TOOTH, PAIN-CHEST, PALPITATIONS, PHLEBITIS LEFT WRIST, SKIN - FACE RASH, SKIN - FLUSHING, SKIN FLUSHING, STOMATITIS, SWELLING RT ARM, FINGERS & TOES, TINNITUS, URINARY FREQ/BURNING, URINARY FREQUENCY/BURNING, WEIGHT LOSS.

   Please clarify the manner in which adverse events were coded such that an investigator verbatim description of an adverse event such as "HYPERTENSION" is unable to be mapped to a preferred adverse event term?

2. Please clarify the rationale for coding the following adverse event in subject 45346 as a Venous Thromboembolic Event.

Description and Treatment of Event(s):	Patient was admitted after a left ventricular thrombus was incidentally identified on chest CT. Subsequent echocardiogram was performed that confirmed a left apical thrombus associated with left apical akinesis and aneurysm. There was also severe reduction of left ventricular systolic function with multiple wall motion abnormalities. Patient was admitted for anticoagulation due to the thrombus and left ventricular aneurysm.		
Present Status :	Intervention for AE Continues	**Date of Recovery or Death :**	
Retreated :	No		
Removed from Protocol Treatment (to date):	Yes	**Date Removed from Protocol Treatment :**	11/18/2003
Death Date :		**Autopsy Performed :**	No

Were the CRFs reviewed for "other significant adverse events" in order to confirm the nature of the event prior to creating the tables for the CSR and data used for the calculation of incidence rates of adverse events for the proposed PI? Please clarify the Standard Operating Procedure Genentech employs when analyzing data for either FDA or Genentech determined "significant adverse events".

3. Please clarify if the variable name AETIME as defined below should correlate closely with a "Yes" in the variable name column AECYC6 if the AETIME is less than 18 weeks. Please explain why AETIME periods as short as 3 weeks are associated with a "NO" in the AECYC6 data column as can be seen below in the ADV adverse event data set.

AECYC6	AE Recorded Prior to or on Cycle 6	Char		Derived	Values: 'YES', 'NO', or missing. If Adverse Event Raw Term (AE.AETERM) is non-missing and within the first 6 cycles (0 <= AE.VISITNUM <= 1006) set to 'YES'; else if Adverse Event Raw Term is non-missing and after the first 6 cycles (AE.VISITNUM > 1006) set to 'NO'; else set to missing. Not collected for EPP patients.
AETIME	Time First Dose to Start AE Rpt Per(Wks)	Num		Derived	The difference, in weeks, between first dose date (AE.FSTTXDT) and AE reporting period start date (AE.AERBDT).

b(4)

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Tuesday, August 01, 2006 4:01 PM
To: 'hunte@gene.com'
Subject: clinical IR for STN 125085/85 (NSCLC)

Attachments: Picture (Enhanced Metafile)

The following is reproduced from page 129 of the CSR for Study E4599:

> Deaths categorized as due to a cause other than those due to NSCLC included the following:
>
> - CP arm (15 patients) includes: myocardial infarction (3 patients); anoxic encephalopathy (description of death included respiratory arrest, metastatic cancer, and adenocarcinoma lung); respiratory failure; cerebrovascular accident (CVA; 2 patients); chronic obstructive pulmonary disease; injuries sustained from car accident; malignant disease (colon cancer); pneumonia (2 patients); pulmonary embolism; and suicide (2 patients).
> - BV/CP arm (23 patients) includes: acute cortical stroke; myocardial infarction (3 patients); cardiogenic shock secondary to myocardial ischemia, pneumonia (4 patients); cardiac disease (unspecified); cardiac arrest; CVA (2 patients); complications from extrapleural pneumonectomy; cardiopulmonary arrest secondary to congestive heart failure and coronary artery disease; comorbidities/failure to thrive; gross hematemesis and melena; hemorrhage (unspecified); perforated viscus (tumor) associated with sepsis/septic shock; progressive chronic obstructive pulmonary disease; fevers of unknown origin; pulmonary embolism; and trauma to head secondary to fall at home.

FDA has identified the total number of deaths not listed as "unknown" or "due to this disease" in the DEATH data set provided for review as follows:

CP arm 18 subject deaths: (Patient Identification Numbers) 45128, 45167, 45208, 45217, 45276, 45283, 45381, 45400, 45413, 45436, 45455, 45509, 45533, 47019, 47059, 47065, 50091, and 52007.

BV/CP arm: 30 subject deaths: (Patient Identification Numbers) 45011, 45017, 45027, 45050, 45095, 45098, 45132, 45134, 45145, 45154, 45160, 45171, 45284, 45315, 45322, 45324, 45325, 45353, 45379, 45396, 45513, 45593, 47010, 47043, 50001, 50012, 50056, 50059, 52026, and 53011.

Please clarify the reasons for the discrepancy between Genentech's and FDA's analysis of total number of deaths due to causes other than NSCLC.

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Monday, July 31, 2006 3:53 PM
To: 'hunte@gene.com'
Cc: 'Lisa Bell'
Subject: IR for STN 125085/85 (NSCLC)

Attachments: 7-31-06 IR.doc

Is attached.

7-31-06 IR.doc (46 KB)

1. Please clarify the coding for STFWTLSC. If the coding is reversed, the results will not be the same as those stated in the study report (e.g., Table 8). The coding for STFWTLSC seems to match the baseline variable WGTLGP, except a coding difference ('YES' is for >=5% in WGTLGP, but is >5% in STFWTLSC).

2. Please also provide a revised variable STFWTLSC based on the following definition :

   Baseline weight loss ≥ 5% =YES and <5% = NO.

   Currently it is defined as >5% = YES and ≤ 5% = NO.

3. In Table 5 of the E4599 study report, ECOG eligibility evaluation forms were found to be missing in 39 out of 444 PC patients and 43 out of 434 PC/BV arm. The stratification error was only identified in 7/405 patients of the PC arm and 10/434 patients in the PC/BV arm. Based on a cross-tabulation of these stratification factors with the baseline variables from demographic page (see attached), discordant pairs seem more than those stated in the stratification error of Table 4 (see the numbers highlighted in purple in the attached document). Please clarify the following questions:

   a. Please describe the consolidation procedure that had been performed to resolve the difference in the tumor measurability, prior radiotherapy and weight loss between data collected via ECOG eligibility evaluation form and data collected in the ECOG Case Evaluation Forms. Please explain the discrepancy in terms of the difference in

      PRIRADIO vs. STFPRXC
      DISMEAS vs. STFMEASC
      WGTLGP vs. STFWTLSC,

      As shown in the tables attached.

   b. If data from the ECOG eligibility evaluation form are missing, please describe how complete data in all three stratification factors were obtained. Currently there are no missing data in tumor measurability, prior radiotherapy and weight loss based on stfprxc (stfprxn), stfprxc (stfprxn) and stfwtlsc (stfwtlsn).

   c. Please update your database to reflect the correct coding for the following variables for archival purpose :

      STFPRXC
      STFMEASC
      STFWTLSC.

Attachment :

Note : STFPRXC and STFMEASC should be recoded, i.e. change 'YES' to 'NO' and 'NO' to 'YES'.

Table of PRIRADIO by STFPRXC

PRIRADIO(Prior Radiotherapy (YES, NO))
STFPRXC(Stratify Factor: Prior Radiation (char))

Frequency, NO	YES	Total
	0 3	3
NO	771	795
YES	75	80
Total	99 779	878

Table of DISMEAS by STFMEASC

DISMEAS(Disease Measurable (YES, NO))
STFMEASC(Stratify Factor: Tumor Measurable (char))

Frequency, NO	YES	Total
	1 0	1
NO	61	77
YES	772	800
Total	789 89	878

Table of WGTLGP by STFWTLSC

WGTLGP(Wt Loss in Prev 6 Mos >= 5% (YES, NO))
STFWTLSC(Stratify Factor: Weight Loss > 5% (char))

Frequency, NO	YES	Total
6	1	7
NO 608	[redacted]	624
YES [redacted]	201	247
Total 660	218	878

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125085/85

JUN 09 2006

Genentech, Incorporated
Attention: Robert L. Garnick, Ph.D.
Senior Vice President, Regulatory Affairs, Quality and Compliance
1 DNA Way, MS #242
South San Francisco, CA 94080-4990

Dear Dr. Garnick:

This letter is in regard to your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplement dated April 10, 2006, for Bevacizumab to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your supplement today. The user fee goal date is October 11, 2006. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified the following potential review issues which were previously communicated to you via facsimile on May 30, 2006.

1. Please arrange for a limited audit of the objective response rate (ORR) data in Study E4599 and conduct an independent, blinded, adjudicated review of the complete series of radiology imaging assessments used for determining and confirming objective response from the following 21 subjects:

   - Mayo Clinic/Illinois Oncology Research Associates: 45016, 45047, 45059, 45117, 45120, 45121, 45267, 45327, 45377, 45378, and 45501.
   - Indiana University Medical Center/Rush Presbyterian St. Luke's Medical Center: 45197, 45225, 45426, 45511, and 45557.
   - Northwestern University/Ingalls Medical Center: 45010, 45133, 45187, 45291, and 45566.

   The independent ORR radiology audit should include a description of the independent read procedure used for the audit of the ORR data and an analysis of the following:

   a. The onsite read process that was employed at the selected sites.

b. The consistency and uniformity of imaging acquisition used across the three selected sites.

c. The amount of missing time-points and poor scan quality.

Please notify us within two weeks of your timetable to fulfill this request. If you are unable to make these arrangements in a timely manner, please so state. Alternatively, you may submit revised labeling removing these claims from the proposed physician package insert.

2. Please construct and provide by June 12, 2006, a single adverse event dataset that includes all sources of adverse event collection including the E4599 toxicity form, Off Study Forms, AdEERS, and MedWatch Reports. Please design the dataset so that the collection source is identified and searchable.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 796-2320.

Sincerely,

Patricia Keegan

Patricia Keegan, Ph.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Filing Notification (FL) &
Deficiencies (DI)

SS Data Check:

- **Communication**
- **Milestone: Confirm Filing Action Entry & Close Date**
- **If applicable – Confirm Deficiencies Identified Entry & Close Date**

cc: DBOP/J. Summers
DBOP/J. Gootenberg
DBOP/P. Keegan
DBOP/S. Sickafuse
OBS/M. Rothmann
OBS/Y. Shen
DDMAC/C. Broadnax
DSI/R. Young
OODP/K.Weiss
OODP/R. Pazdur
HFD-005/Mike Jones
Office of Medical Policy/R. Temple
DRMP BLA file (hard copy)
HFD-020/ Immediate Office (hard copy)

History: Sickafuse:6-2-06:6-5-06:6-8-06: K. Townsend: 6.8.2006

File Name: N:DBOP/Sickafuse/Bevacizumab/efficacy supplements/125085_85/filing letter.doc

Division	Name/Signature	Date
DBOP	Sickafuse	6-8-06
OODP/DBOP	Karen D. Jones	6-8-06
DBOP	Patricia Keegan	6-9-2006
DBOP	Kelly Townsend	6/9/06

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0933
RECIPIENT ADDRESS	916502253512
DESTINATION ID	
ST. TIME	05/30 14:04
TIME USE	01'10
PAGES SENT	2
RESULT	OK

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF NEW DRUGS

OFFICE OF ONCOLOGY DRUG PRODUCTS

DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS

White Oak Office Complex – Building 22
10903 New Hampshire Avenue
Sliver Spring, Maryland 20993
FAX #: 301-796-9849

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 2 (Including Cover Page)

FAX TO: Brisdell Hunte

650-225-3512 Facsimile Telephone No. 650-225-6829 Voice Telephone No.

FROM: Sharon Sickafuse

Facsimile Telephone No. Voice Telephone No. 301-796-2320

DATE: 5-30-06 **TIME:**

MESSAGE: Information request for STN 125085/85.

May 30, 2006, Information Request for STN 125085/85

1. Please arrange for limited audit of the objective response rate (ORR) data in Study E4599 and conduct an independent, blinded, adjudicated review of the complete series of radiology imaging assessments used for determining and confirming objective response from the following 21 subjects:

   - Mayo Clinic/Illinois Oncology Research Assoc. 45016, 45047, 45059, 45117, 45120, 45121, 45267, 45327, 45377, 45378, 45501
   - Indiana University Medical Center/Rush Presbyterian St Luke's Medical Center 45197, 45225, 45426, 45511, 45557
   - Northwestern University/Ingalls Medical Center 45010, 45133, 45187, 45291, 45566

   The independent ORR radiology audit should include a description of the independent read procedure used for the audit of the ORR data and an analysis of the following:

   a. The onsite read process that was employed at the selected sites.

   b. The consistency and uniformity of imaging acquisition used across the three selected sites.

   c. The amount of missing time-points and poor scan quality.

   Please notify us within two weeks of your timetable to fulfill this request. If you will be unable to make these arrangements in a timely manner, please so state.

2. Please construct and provide by June 12, 2006, a single adverse event data set that includes all sources of adverse event collection including the E4599 toxicity form, Off Study Forms, AdEERS and MedWatch Reports. Please design the data set so that the collection source is identified and searchable.

BLA/NDA/PMA
Review Committee Assignment Memorandum

STN: 125085/85

☐ Initial Assignment
☒ Change

Applicant: Genentech, Inc.

Product: Bevacizumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
	Reg. Project Manager	Admin/Regulatory		
	Reviewer	Admin/Regulatory		
		Product*		
	Reviewer	Product*		
	Reviewer	Product		
		Clinical		
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
	Reviewer	Biostatistics		
Robert Young	Reviewer	BiMo	L. Ball	5-9-06
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
	Reviewer	Labeling		
		Other		

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
Lauren Iacono-Connor	Reviewer	BiMo (DSI)	Leslie Ball	5-9-06

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Sharon Sickafuse — Name Printed / Signature

5-9-06 — Date

Memo entered in RMS by: 5/22/06 Date: ____ QC by: ____ Date: ____

BLA/NDA/PMA
Review Committee Assignment Memorandum

STN: 125085/85

☒ Initial Assignment
☐ Change

Applicant: Genentech, Inc.

Product: Bevacizumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Sharon Sickafuse	Reg. Project Manager	Admin/Regulatory	K. Jones	4-17-06
	Reviewer	Admin/Regulatory		
		Product*		
	Reviewer	Product*		
	Reviewer	Product		
Jeff Summers		Clinical	P. Keegan	4-20-06
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
Yuan-Li Shen	Reviewer	Biostatistics	M. Rothmann	4-18-06
Lauren Iaconno-Connor	Reviewer	BiMo	L. Ball	5-2-06
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
Carole Broadnax	Reviewer	Labeling	J. Wang	4-17-06
		Other		

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Sharon Sickafuse — 5-2-06

Name Printed — Signature — Date

Memo entered in RMS by: _____ Date: _____ QC by: _____ Date: _____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Genentech, Incorporated
Attention: Robert L. Garnick, Ph.D.
Senior Vice President, Regulatory Affairs, Quality and Compliance
1 DNA Way, MS #242
South San Francisco, CA 94080-4990

APR 28 2006

Dear Dr. Garnick:

SUBMISSION TRACKING NUMBER (STN) BL 125085/85 has been assigned to your recent supplement to your biologics license application for Bevacizumab received on April 11, 2006, for use as first-line treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer in combination with platinum-based chemotherapy.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on February 26, 2004, for the pediatric study requirement for this application.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Sharon Sickafuse, at (301) 796-2320.

Sincerely,

Karen D. Jones

Karen D. Jones
Chief, Project Management Staff
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Acknowledgment Letter (ACK)
Summary Text: (PAS)

SS & RIS Data Check:
- **If "Unacceptable for Filing" add 2nd LETTER TYPE "UN".**
- **Communication**

RIS Data Check:
- **Submission Screen: In Arrears Box Is Checked**
- **Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match**
- **No Action Due Date**
- **STN Status – Unacceptable for Filing**

cc: Sharon Sickafuse
Jeff Summers
HFD-141/Ayoub Suliman
DBOP BLA file (hard copy)

History: K. Townsend: 4.26.2006

File Name: N:\DBOP\STN 2006\125085.85.PAS.doc

Division	Name/Signature	Date
DBOP	Sic Kafuse	4-27-06
ODDP/DBOP	Karen D. Jones	4-27-06
ODSP/DBOP	Kelly Lawrence	4/28/06

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 20, 2006

From: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products

Subject: Designation of Priority for Supplemental BLA Review
Sponsor: Genentech, Inc..
Product: Bevacizumab
Indication: First line treatment of locally advanced, metastatic or recurrent non-small cell lung cancer in combination with platinum-based chemotherapy

To: STN 125085/85

The review status of this file is designated to be:

□ Standard (10 mon.) X Priority (6 mon.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 11, 2005

From: Sharon Sickafuse, CDER/ODE6/DRMP

To: IND 8648

Subject: July 21, 2005, teleconference with Genentech regarding the sBLA for NSCLC

Teleconference Date: July 21, 2005

Teleconference Requestor: Genentech, Inc.

Product: Bevacizumab

Proposed Use: Treatment of non-small cell lung cancer (NSCLC) in combination with platinum-containing chemotherapy

Teleconference Purpose: Discuss sBLA for this indication. Primary study data is from study E4599.

Background: Teleconference package is amendment 569 submitted on June 21, 2005. FDA responses to Genentech's questions were faxed to them on July 21, 2005. Below are Genentech's questions, FDA responses and the discussion that occurred during the teleconference.

1. *Based on the significant survival results and the safety profile observed with bevacizumab in Study E4599 and additional efficacy and safety from Study AVF0757g, Genentech believe that the results from these two trials are sufficient to support a sBLA to extend the current indication for Avastin to the following: "Avastin, used in combination with platinum-based chemotherapy, is indicated for the first line treatment of patients with advanced or recurrent, non-squamous non-small cell lung cancer." Does the Agency agree that these two studies form the basis for this sBLA?*

   FDA agreed that studies E4599 and AVF0757g are sufficient to form the basis of an sBLA, however FDA cannot comment upon the indication statement prior to review of the submitted data.

2. *Does the Agency agree that the ECOG DMC interim analysis will form the primary basis for assessing statistical significance of the overall survival endpoint?*

FDA agreed that the results of the two interim analyses for overall survival will form the basis for assessing statistical significance (i.e., for determining the final p-value). Any later analysis will be for descriptive purposes only.

FDA asked Genentech to provide the results of the first interim analysis (including the timing of the analysis), the specific rule that was used for the timing of the analysis and the spending function that was used. Please also provide the timings (dates and number of events) of any informal interim analysis.

Discussion: Genentech agreed to provide the requested information. FDA asked if the patient population for the primary analysis will be the eligible population or the intent-to-treat population. Genentech stated that they will perform analyses with both populations, however the analysis on the intent-to-treat population (all randomized patients) will be the primary analysis.

3. *Does the Agency agree with Genentech's proposal for submission of the Clinical Study Report, patient narratives, Case Report Forms, and Case Report Tabulations?*

	Genentech Proposal	FDA
Patient Narratives	Experimental arm only Deaths-deaths < 30 d not due to PD and deaths > 30 d if thought due to bevacizumab AdEERs Report of Gr 3-4 AEs Gr 3-4 GI perforation or fistula Gr 1-4 Arterial TE Event Gr 3-4 Hemorrhage Secondary Malignancy Discontinuation due to AE	Narratives only for pts in the experimental arm Please also include narratives for CHF, gr 3-4 neuropathy, gr 3-4 HTN, and gr 3-4 proteinuria in the experimental arm.
CRFs	Pts requiring a narrative	CRFs for who die or discontinue therapy in both arms All CRFs should be available on request
SAS Datasets	All data collected on CRFs	Agree
SAS Programs	No Will provide variable derivations	Programs for primary and secondary analyses Programs for creating the derived datasets.

Discussion: Genentech agreed to provide all information requested by FDA as described in the table above.

- FDA asked that the programs used to create the derived datasets from the raw datasets be submitted. If these programs are not submitted and the FDA analyses based on the raw data lead to different results from those submitted results, the official results will be those from the FDA analyses.

Discussion: Genentech agreed to provide the programs used to create the derived datasets from the raw datasets.

- FDA advised that the inclusion of narratives from patients only in the experimental arm may negatively impact the adverse event profile of Bevacizumab by providing insufficient information for comparison to the control arm. In the absence of narratives from the control arm, all events will be attributed to Bevacizumab.

Discussion: Genentech expressed understanding, but still elected not to provide patient narratives for the control arm.

- FDA recommended that narratives should be based on information reported in both AdEERs and the clinical database. Please highlight discrepancies in the information provided in these two databases and included within a narrative.

Discussion: Genentech agreed to do so.

- FDA asked that narratives for adverse events leading to discontinuation list all adverse events that occurred within 30 days of discontinuation.

4. *Does the Agency agree with the proposed metadata for the datasets and statistical analyses to be submitted to the Agency?*

   FDA agreed and stated that there are a number of questions concerning the details of these datasets that can be discussed separately. Update: Teleconference held on July 27 2005, between Genentech representatives and Drs. Maher, Summers, and Rothmann.

5. *Does the Agency agree with Genentech's proposal for the Summary of Clinical Efficacy?*

   FDA agreed.

6. *Does the Agency agree with Genentech's proposal for the Summary of Clinical Safety?*

   FDA agreed and understands that there will be no pooling of safety data of study E4599 and study AVF0757g.

7. *Assuming there are fewer than five patients receiving study drug at the time of filing, Genentech does not intend to submit a Safety Update to the sBLA. Does the Agency agree with this proposal?*

FDA asked Genentech to clarify whether this represents the number of patients receiving treatment at the time of database lock or at the time of filing.

Discussion: Genentech stated that as of July 21, 2005, approximately 10 patients are still receiving treatment. FDA recommended that Genentech provide a safety update including all serious adverse events which have occurred since the time of database lock. It is not necessary to recalculate each adverse event. Genentech agreed to provide a Safety Update.

8. *Based on the significant survival results and the safety profile observed with bevacizumab, Genentech believes that this sBLA is eligible for priority review. Does the Agency agree with this proposal?*

FDA agreed.

9. *Given the strength of the survival data and the known safety profile of bevacizumab, does the Agency agree that an Oncologic Drug Advisory Committee meeting is unnecessary?*

FDA stated that the need for an Advisory Committee meeting cannot be commented upon prior to review of the submission.

Additional FDA Comments:

10. Please provide additional information (such as mock up tables or listings) concerning the planned highlighting of adverse events that are only reported in AdEERs or only in the clinical database.

Discussion: FDA requested that the AdEERs information be in SAS format, not as a narrative across multiple columns as in the TRC supplement. FDA also asked that Genentech explain the sources of supportive information in AdEERs. Genentech agreed to submit examples by the end of August of the way in which they intend to highlight differences in the AdEERs and clinical databases.

11. The pre-teleconference package contains a proposal to omit several of the analyses agreed to in the final statistical analysis plan. This is acceptable only if the datasets necessary to perform these analyses, along with appropriate flags, are included in this supplement. Early participation in this effort may facilitate the review process, especially if FDA analyses generate results on which Genentech would like to provide comment during the review.

Discussion: Genentech agreed to provide the datasets.

12. Under 21 CFR 314.50 (k) Genentech is required to act with due diligence to obtain the information necessary for financial disclosure certification. Given that all of the necessary documents were in fact collected, the proposal to include only documents collected after March 2002 does not meet the standard of due diligence.

Discussion: Genentech agreed to submit all financial disclosure information.

13. Please include all lot numbers and their site of manufacture in your submission.

Discussion: Genentech agreed to provide this information.

14. Prior to filing, please provide the following information, in tabular format, for each site.

Site #	# Screened	# Enrolled	# Deaths	# Discontinued	# SAEs	# Major Protocol Violations	Response Rate

Discussion: Genentech and ECOG said that the sites don't record the number of patients screened and FDA agreed that this information could be omitted from the above table. Genentech and ECOG also stated that events are not listed as serious in their database. FDA asked if they could provide the number of Grade 3-4 events rather than the number of serious events by site. They will be able to do so. FDA was concerned that the same patient may be counted multiple times (i.e, if the same patient had a Grade 4 event, discontinued, and later died) and may not provide a true picture of the toxicity at that site. FDA asked if Genentech could provide an additional column with a per patient incidence of these events at each site. Genentech agreed.

15. If IRB approvals and CVs are not included in the supplement, please provide a letter of cross reference to the NCI master file or IND where this information resides. In this letter, you will need to specify the date of submission, the volume number, and the page number.

FDA Attendees:

Center for Drug Evaluation and Research

Office of Oncology Drug Products
Division of Biologic Oncology Products
Patricia Keegan, M.D.
Ellen Maher, M.D.
Sharon Sickafuse, M.S.
Jeff Summers, M.D.

Office of Biostatistics
Biologic Therapeutic Statistical Staff
Mark Rothmann, Ph.D.

Sponsor Attendees:

Genentech, Inc.

Lisa Bell, Ph.D., Senior Manager, Regulatory Affairs
Isaiah Dimery, M.D., Director, BioOncology
Benjamin Lyons, Ph.D., Senior Biostatistician, Biostatistics
Sandra Minjoe, M.S., Principal Statistical Programmer Analyst, Statistical Programming
Michael Ostland, Ph.D., Associate Director, Biostatistics
David Ramies, M.D., Medical Director
Todd Rich, M.D., VP of Medical Affairs
Michelle Rohrer, Ph.D., Director, Regulatory Affairs
Jamey Skillings, M.D., Group Director, BioOncology
Kathleen Winson, M.A., Operations Team Leader, BioOncology

ECOG

Robert Gray, Ph.D., Group Statistician
Alan Sandler, M.D., Study Chair
Joan Schiller, M.D., Thoracic Committee Chair

NCI

Helen Chen, Senior Investigator, CTEP
Scott Saxman, M.D., Senior Investigator, Clinical Investigations Branch, CTEP, DCTD

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: September 29, 2004

From: Sharon Sickafuse, CDER/ODE6/DRMP

To: IND 7023

Subject: September 2, 2004, meeting with Genentech regarding the statistical analysis plan (SAP) for study E4599

Meeting Date: September 2, 2004

Meeting Requestor: Genentech, Incorporated

Product: Bevacizumab

Proposed Use: Treatment of non-small cell lung cancer (NSCLC)

Meeting Purpose: Discuss the SAP for study E4599 "Randomized Phase 2/3 Trial of Paclitaxel Plus Carboplatin with or without Bevacizumab in Patients with Advanced Nonsquamous NSCLC". This study is being conducted by NCI under their IND. Meeting package is amendment 470.

FDA draft responses to Genentech's questions (Appendix A) were faxed to Genentech on September 1, 2004.

Sponsor Questions and FDA Responses:

1. *Does the Agency concur with the content of the Statistical Analysis Plan for Study E4599?*

   FDA recommended further revisions to address the following comments:

   - Specific rules for the timing of the formal interim and final analyses should be provided and followed without exception. FDA asked when the formal interim analysis will occur. Is this analysis by a certain date or after a specific number of events? Genentech replied that the first interim analysis will occur at the Data Monitoring Committee (DMC) meeting scheduled for November 1, 2004. The cut-off date for data for this analysis is 8 weeks prior to the meeting. A formal interim analysis will occur the first time when the number of events by

the cut-off date is greater than 5% less than the pre-specified number of events for that formal interim analysis. The cut-off date for the final analysis will be based on the pre-specified number of events.

- In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints can not result in (either singly or in combination) an efficacy claim for reasons discussed further below (see Additional Comments). In the event that there is a statistically significant result for the primary analysis of the primary endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future revised SAP, any secondary endpoints for which claims may be included in the labeling and how adjustments will be made for multiplicity to guarantee an overall 0.05 level for the tests of such secondary endpoints.

  Genentech agreed to do so. The secondary endpoints are response rate and progression free survival (PFS) in that order. A hierarchical testing procedure for the secondary endpoints will first compare response rates. FDA stated that this proposal is acceptable.

- For overall survival, a sensitivity analysis that would be a "worst case" comparison (instead of a comparison of the "worst possible case"), may treat patients on arm B who were lost to follow-up as having their date of death be considered as their last contact date plus 1 and patients on arm A who were lost to follow-up as having their overall survival censored at the date of last contact.

  Genentech will do this.

- FDA stated that deaths are an endpoint and should be censored in analyses of PFS. FDA would accept a sensitivity analysis (not the primary analysis) in which those patients where death occurs > 3 months following their final tumor assessment would b3e censored at the time of the most recent tumor assessment. FDA also expressed concerns about the amount of missing assessments/follow-up and asked whether this was the reason for developing a plan for imputation of data in the analysis of PFS.

  Genentech stated that they expect to have all scheduled tumor assessment data on the majority of patients and agreed not to censor death in the primary analysis of PFS.

2. *Based on the Statistical Analysis Plan and responses to the Agency's letter dated 5 June 2003, does the Agency concur that Study E4599 is adequate to support the proposed use of Avastin in combination with chemotherapy for the first-line treatment of patients with advanced or metastatic non-squamous NSCLC?*

FDA stated that based on the SAP and responses to Agency comments contained in amendment 470, we do not concur that study E4599 is adequate to support the proposed use of Avastin in combination with chemotherapy for the first-line treatment of patients with advanced or metastatic non-squamous NSCLC. We would need to be provided the study data in order to make any determination of the adequacy of the study to support this indication. If the data on the primary endpoint of study E4599 are compelling, we would accept the study for review as a component of a licensing supplement.

FDA emphasized that we need to see the E4599 auditing results to determine how well the study was conducted. ECOG said that they review the data from each institution, but the reviews are not blinded. In addition, monitoring groups go to each site and verify the data. Sites are audited every 3 years. Ten percent of an institution's patients are audited and many times for large institutions, 15% of the patients are audited. FDA would like to see the results of these audits.

FDA stated that internal consistency in all the study endpoints is preferable as well as having a survival advantage associated with an anti-tumor effect.

In light of the results of the Phase 3 breast cancer study, the benefit of Avastin in the treatment of colorectal cancer may not be generalizable to all malignancies. The results of this study may need to be augmented by a second adequate and well controlled study in this subject population.

Additional FDA Comments/Recommendations:

1. The flawed design and variable conduct of the study limits the efficacy data that could be used to support the proposed indication to the survival endpoint only. The secondary endpoints of response rate, duration of response, and progression free survival may not be adequate to be included in labeling because of the following:
   a. The study is not blinded.
      - The pilot study described in section 1.54 of the E4599 study protocol demonstrates the potential for investigator bias that can be present with such a design.
      - The study lacks an independent, blinded review of the data used to determine response rates and disease progression.

b. There is the potential that ascertainment bias will be introduced by the different schedules used for post-chemotherapy tumor assessment between treatment arms A and B.

c. Please note that supplemental approval for this indication may necessitate a post-marketing commitment to conduct one or more adequate and well controlled studies designed to determine the contribution of the continuation of administration of Bevacizumab after completion of cytotoxic chemotherapy in this setting.

Additional Discussion Items:

1. Genentech would like to amend the primary analysis population for objective response rate on page 41 of amendment 470 from all randomized patients to patients with measurable disease. Genentech expects that 80% of the patients will have measurable disease. FDA stated that this was acceptable, but noted that assessment of overall response rate in both populations (all patients and patients with measurable disease) should be reported.

2. In response to FDA's query about other studies relevant to this indication, Genentech stated that Hoffman-La Roche is developing a Phase 2/3 study outside of the U.S. This study will compare two different doses of Bevacizumab plus gemcitabine and cisplatin to chemotherapy alone in nonsquamous NSCLC. There will be 70 patients/arm for a total of 210 patients. Follow-up is 7-8 months. This study may be supportive of the NSCLC supplement. FDA stated that the decision to submit data from this study in support of an efficacy supplement should be re-visited at the time of a pre-sBLA meeting, taking into account the maturity of the study.

Decisions/Agreements Reached:

1. If the data on the primary endpoint of study E4599 are compelling, FDA would accept the study for review as a component of a licensing supplement.

Action Items for Genentech:

1. Submit revised SAP.
2. Provide ECOG's audit of the response data.

Amendment to Minutes Regarding ECOG Auditing Reports:

Based on the September 16, 2004, discussion between FDA and NCI/CTEP regarding auditing reports, FDA acknowledges NCI's statements that the clinical site audits are too fragmentary to provide assurance of adherence to Good Clinical Practices and/or study conduct. In lieu of the request for audit reports from clinical sites participating in E4599, FDA requests that NCI provide a statement that no investigator in the study was removed as an NCI investigator or required to take corrective action as a result of findings on audit.

FDA Attendees:
Center for Drug Evaluation and Research
Office of Drug Evaluation VI

Division of Review Management and Policy
Sharon Sickafuse, M.S.

Division of Therapeutic Biological Oncology Products
Joseph Gootenberg, M.D.
Robert Justice, M.D.
Patricia Keegan, M.D.
Ellen Maher, M.D.
Jeff Summers, M.D.

Office of Biostatistics
Biologic Therapeutics Statistical Staff
Mark Rothmann, Ph.D.

Sponsor Attendees:
Genentech, Inc.
Alex Bajamonde, Ph.D., Director, Biostatistics
Angela Gordon,
Susan Griffing,
Patricia Harada, M.P.H., Manager, Regulatory Affairs
Cheryl Madsen, Senior Manager, Regulatory Affairs
Robert Mass, M.D., Director, Medical Affairs
Michael Ostland, Ph.D., Senior Biostatistician, Biostatistics
Todd Rich, M.D., Senior Director, Regulatory Affairs
Jamey Skillings, M.D., Director, Medical Affairs

Roche
Hans-Ulrich Burger, Ph.D., Biostatistics Section Head

ECOG
Robert Gray, Ph.D., Group Statistician
Joan Schiller, M.D., Chair of the Lung Cancer Committee

CTEP, DCTD, NCI
Jeff Abrams, M.D., Associate Chief, Medicine, Clinical Investigations Branch
Helen Chen, M.D., Senior Investigator, Investigational Drug Branch
Scott Saxman, M.D., Senior Investigator, Clinical Investigations Branch

Attachments:
Attendee list
Appendix A: Draft comments faxed to Genentech on September 1, 2004.