CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125085 / Supp 0074

Trade Name: Avastin

Generic Name: Bevacizumab

Sponsor: Genentech, Inc.

Approval Date: June 20, 2006

Indications: 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

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APPLICATION NUMBER:
BLA 125085 / Supp 0074

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125085/74

JUN 2 0 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

Dear Dr. Garnick:

Your request to supplement your biologics license application for Bevacizumab to expand the indication to include use as an adjunct to chemotherapy for the second-line treatment of patients with metastatic colorectal cancer, has been approved.

This fulfills your commitment to provide the final study report for study E3200, examining the comparative safety and effectiveness of single agent Bevacizumab, Bevacizumab in combination with the FOLFOX4 regimen, and FOLFOX4 alone as stated in commitment number 17 of the February 26, 2004, approval letter.

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 until December 31, 2006.

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 June 19, 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).

Please submit 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 June 19, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

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 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

Enclosure: Revised Labeling dated 6-19-06

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)
LETTER: Fulfillment of PMC (FPC)
Summary Text: Clinical Supplmt. Efficacy - New/Expanded Indication
LETTER: Pediatric Deferral Granted (PDG)

REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:
- Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).

RIS Data Check:
- Verify short summary – Ltr. & Submission screen should match.
- Check Letter for PMCs (if PMCs – add "PMCs – Approved With" special characteristic code.)
- Check if Major Approval – if so – add code.
- Perform Review Completion Process
- Milestone: Confirm Approved Status

cc: OODP/K. Weiss
OODP/R. Pazdur
OODP/G. Jones
DBOP/S. Sickafuse
DBOP/J. Summers
DBOP/J. Gootenberg
DBOP/P. Keegan
DBOP/C. Lee
OBS/M. Rothmann
OBS/Y. Shen
HFM-110/RIMS/R. Eastep
OND/John Jenkins
OND/Exec sec V. Kinsey
OND/C. O'Leary
HFD-005/Mike Jones
HFD-410/ODS/DSRCS(Medwatch)/K. Young
ODS/DDRE/R. Pratt
HFD-013/FOI/C. Doyle
HFD-013/FOI/A. Glover
HFD-240/OTCOM/ B. Poole
HFD-230/OTCOM/CDER WebMaster
HFI-20/Press/ L. Gelb
HFI-20/Press/ J. Brodsky
DDMAC/K. Gray
DDMAC/C. Broadnax
CDER-OCTAP960PM (PEDs e-mail account)

HFD-322/IPCB/E. Rivera-Martinez
HFD-123/DMA/K. Clouse
HFD-328/TFRB Blue File/Mike Smedley
OBP/S. Kozlowski
DBOP BLA file (hard copy)

History:Sickafuse:5-16-06:6-13-06: K. Townsend: 6.14.2006

File Name: N:DBOP/Sickafuse/Bevacizumab/efficacy supplements/125085_74/approval letter.doc

Division	Name/Signature	Date
DBOP	Sickafuse	6-20-06
OODP/DBOP	Karen D. Jones	6/20/06
DBOP	P. Keegan	6-20-06
OODP/DBOP	K. Laudano	6/23/06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 125085 / Supp 0074

LABELING

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 receiving AVASTIN was 2.4%. 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

Serious, and in some cases fatal, hemoptysis has occurred in patients with non–small cell lung cancer treated with chemotherapy and AVASTIN. In a small study, the incidence of serious or fatal hemoptysis was 31% in patients with squamous histology and 4% in patients with adenocarcinoma receiving AVASTIN as compared to no cases in patients treated with chemotherapy alone. Patients with recent hemoptysis should not receive AVASTIN. (See **WARNINGS: 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

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.

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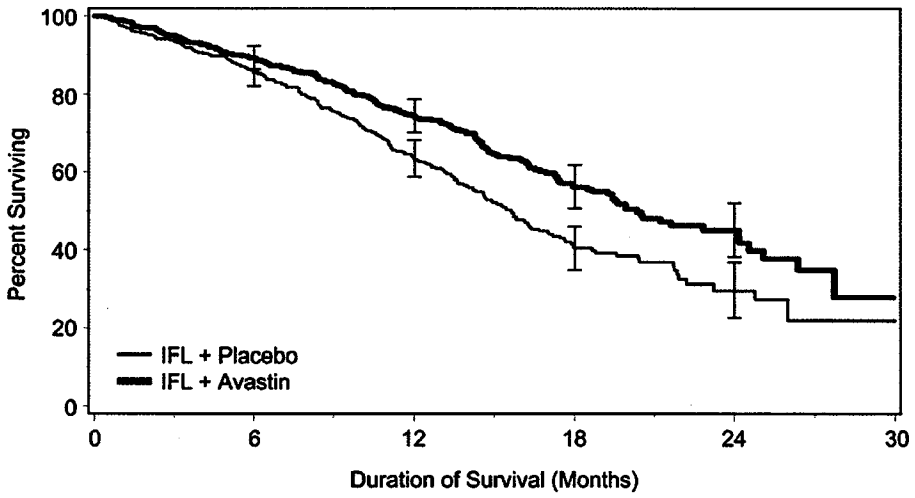
126 **Figure 1**

127 Duration of Survival in Study 1



128

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, 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 FOLFOX4 alone arm. In the two remaining study arms, overall survival (OS) was

significantly longer in patients receiving AVASTIN in combination with FOLFOX 4 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 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%).

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.

CONTRAINDICATIONS

There are no known contraindications to the use of AVASTIN.

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 postmarketing 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 Grade 1 epistaxis. The second is serious, and in some cases fatal, hemorrhagic events. Serious hemorrhagic events occurred primarily in patients with non–small cell lung cancer, an indication for which AVASTIN is not approved.

In a randomized study in patients with non–small cell lung cancer receiving chemotherapy with or without AVASTIN, four of 13 (31%) AVASTIN-treated patients with squamous cell histology and two of 53 (4%) AVASTIN-treated patients with non-squamous histology experienced life-threatening or fatal pulmonary hemorrhage as compared to none of the 32 (0%) patients receiving chemotherapy alone. Of the patients experiencing events of life-threatening pulmonary hemorrhage, many had cavitation and/or necrosis of the tumor, either pre-existing or developing during AVASTIN therapy. These serious hemorrhagic events occurred suddenly and presented as major or massive hemoptysis. Do not administer AVASTIN to patients with recent hemoptysis.

Other serious bleeding events reported in patients receiving AVASTIN included gastrointestinal hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke.

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.

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

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

In a pooled analysis of randomized, controlled clinical trials involving 1745 patients, the incidence of arterial thromboembolic events 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 arterial thromboembolic events 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 arterial thromboembolic event has not been studied. Permanently discontinue AVASTIN in patients who experience a severe arterial thromboembolic event during treatment.

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 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 (see **PRECAUTIONS, Infusion Reactions**). 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.

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 and 3, the incidence of

NCI-CTC Grade 3 and 4 proteinuria, characterized as >3.5 gm/24 hours, ranged up to 1.8% in AVASTIN-treated patients.

Nephrotic syndrome occurred in five of 1032 (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

Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left ventricular dysfunction, was reported in 22 of 1032 (2%) 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 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

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 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.

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 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.

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 REACTIONSThe 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)**
- 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 1106 patients, including 506 receiving AVASTIN® for at least 6 months and 147 receiving AVASTIN® for at least one year. AVASTIN® was studied primarily in placebo- and active-controlled trials (n = 501, and n = 605, respectively). Among 569 patients with metastatic colorectal cancer (mCRC) receiving first-line therapy for metastatic disease, 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. Most patients received doses of 5 mg/kg every 2 weeks; all patients received concurrent chemotherapy. Among 537 patients with metastatic colorectal cancer (mCRC) receiving second-line therapy for metastatic disease, 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, 80% received prior adjuvant chemotherapy, and 99% received prior chemotherapy for metastatic colorectal cancer. Patients received doses of 10 mg/kg every 2 weeks, alone (n=244) or with chemotherapy (n=293).

Gastrointestinal Perforation

Across all studies, the incidence of gastrointestinal perforation, in some cases fatal, in patients with metastatic colorectal cancer (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 ranged from 0 – 3.7%.

Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients receiving AVASTIN. 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

In clinical studies of CRC, both serious and non-serious hemorrhagic events occurred at a higher incidence in patients receiving AVASTIN. (See **WARNINGS: Hemorrhage**.)

In Study 3, the incidence of NCI-CTC Grade 3–5 bleeding events was increased in patients receiving AVASTIN with chemotherapy (5.2%) and in those receiving AVASTIN alone (3.8%) compared to patients receiving FOLFOX4 alone (0.7%). Two patients receiving AVASTIN had fatal CNS hemorrhage.

In Study 1, the incidence of epistaxis was higher (35% vs. 10%) in patients 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%).

Venous Thromboembolic Events

In Study 1, the incidence of NCI CTC grade 3-4 venous thromboembolic events was slightly higher in patients receiving AVASTIN with chemotherapy as compared to those receiving chemotherapy alone. In addition, the risk of developing a second thromboembolic event in patients receiving AVASTIN and chemotherapy is increased compared to patients receiving chemotherapy alone who have experienced a venous thromboembolic event.

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 Grade 3-4 venous thromboembolic events in Study 1was 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 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

The incidences of hypertension and of severe hypertension were increased in patients receiving AVASTIN in Study 1 (see Table 4).

Table 4
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 FOLFOX 4.

Fatal CNS hemorrhage complicating hypertension can occur.

Proteinuria

See WARNINGS and DOSAGE AND ADMINISTRATION: Dose Modifications

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.

First-Line Treatment of Metastatic Carcinoma of the Colon and Rectum

The data in Tables 5 and 6 were obtained in Study 1. All NCI-CTC Grade 3 and 4 adverse events and selected Grade 1 and 2 adverse events (hypertension, proteinuria, thromboembolic events) were reported for the overall study population. In Study 1, the median age was 60, 60% were male, 78% had colon primary lesion, and 29% had prior adjuvant or neoadjuvant chemotherapy. The median duration of exposure to

AVASTIN in Study 1 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 5.

Table 5
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)
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.

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 6.

Table 6

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 6 (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%)

Second-Line Treatment of Metastatic Carcinoma of the Colon and Rectum

The data in Table 7 were obtained in Study 3. 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 7. These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 3.

Table 7
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%)

Other Serious Adverse Events

The following additional serious adverse events occurred in at least one subject treated with AVASTIN in clinical studies.

Body as a Whole: polyserositis

Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic ulceration

Hemic and lymphatic: pancytopenia

Metabolic and nutritional disorders: hyponatremia

OVERDOSAGE

The maximum tolerated dose of AVASTIN has not been determined. 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

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 until disease progression.

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.

Do not initiate AVASTIN until 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. (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 2–8°C (36–46°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

7455305
LV0017
4833702
FDA Approval Date: September 2005
Code Revision Date: September 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 125085 / Supp 0074

MEDICAL REVIEW(S)

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:	125085.74
Drug Name:	Avastin/bevacizumab
Indication(s):	Colorectal carcinoma, second line
Applicant:	Genentech
Date(s):	Submission Date: 15-DEC-05, PDUFA Date: 20-JUN-06, Review Completion Date: 20-JUN-06
Review Priority:	Priority
Medical Division:	Division of Biological Oncology Products (HFD-107)
Clinical Reviewer	Jeff Summers, M.D.
Clinical Team:	Jeff Summers, MD, Joe Gootenberg, MD, Pat Keegan, MD
Project Manager:	Sharon Sickafuse
Biometrics Division:	Biologics and Therapeutics Statistical Staff (HFD-711)
Statistical Reviewer:	Yuan Li Shen,Ph.D
Concurring Reviewers:	Mark Rothmann, Ph.D, Statistical Team Leader, Aloka, Chakravarty, Ph.D., Director

CLINICAL REVIEW

Application Type:	BLAs
Submission Number:	125085.74
Submission Code:	
Letter Date:	12/15/05
Stamp Date:	
PDUFA Goal Date:	6/20/06
Reviewer Name :	Jeff Summers M.D.
Review Completion Date :	6/20/06
Established Name:	Bevacizumab
Trade Name:	Avastin
Therapeutic Class:	TBP Anti-angiogenic
Applicant:	Genentech
Priority Designation:	P
Formulation:	Single use vial for IV administration
Dosing Regimen:	10 µg/kg q 2 weeks
Indication:	[redacted] b(4)
Intended Population:	[redacted]

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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 125085.74 for the use of Avastin at the recommended dose combined with FOLFOX4 chemotherapy as second line treatment to prolong survival in patients with recurrent, advanced, or metastatic colorectal cancer. Modifications, as contained herein, to the Sponsor proposed label are required.

1.2 Recommendation on Postmarketing Actions

No significant safety signals were identified in Study E3200 that would entail additional postmarketing studies to be conducted.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments of the Applicant will be required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical program leading to this submission consisted of a single ECOG conducted, randomized, three arm, open-label, active-controlled study to evaluate the efficacy and safety of FOLFOX versus FOLFOX plus bevacizumab versus bevacizumab monotherapy in patients previously treated with irinotecan for advanced colorectal cancer. The primary endpoint of the study was the duration of survival. Eight hundred twenty nine patients were randomized on this study. Bevacizumab, 10 mg/kg, was administered intravenously every two weeks either alone or in combination with the FOLFOX4 chemotherapy regimen until disease progression or two cycles beyond a complete response. During the April 22, 2003 ECOG DMC meeting, an interim analysis of efficacy data suggested a possible decrease in overall survival in the bevacizumab monotherapy arm compared to the other treatment arms and therefore the bevacizumab monotherapy arm was closed to further accrual. The study was initiated in November of 2001, and the data sets used for the trial analysis were current as of August 2005.

The clinical safety component of the study was conducted such that only "related" Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were captured on the ECOG case report forms. The onset date of the adverse event was not collected on the Toxicity CRF and instead the reporting period, ranging from 1-3 months in duration, was recorded. Selected adverse events were reported in an expedited fashion through NCI AdEERS, using reporting requirements that varied by treatment arm, hence; this data is not useful for comparative analysis of adverse event rates between treatment arms.

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 in the FOLFOX4 and FOLFOX4 + bevacizumab arms demonstrated a statistically significant increase in the duration of survival among patients in the FOLFOX4 + bevacizumab arm compared with those in the FOLFOX4 arm ($p = 0.0012$). Median

survival was 10.8 months (95%CI 10.12, 11.86) in the FOLFOX4 arm and 13.0 months (95% CI 12.09, 14.03) in the FOLFOX4 + bevacizumab 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 what was termed a "centralized review process", this consisted of a review of the primary site radiology reports and measurements and did not involve blinded review of tumor assessment imaging studies.

Stratified analysis of PFS for all patients randomized to the FOLFOX4 and FOLFOX4 + bevacizumab arms demonstrated a statistically significant increase in PFS among FOLFOX4 + bevacizumab patients compared with FOLFOX4 patients ($p < 0.0001$). Median PFS was 4.5 months in the FOLFOX4 arm and 7.5 months in the FOLFOX4 + bevacizumab arm. A large proportion of the subjects were censored in the Applicant-provided PFS analysis for inadequate assessment after coming off of study for toxicity reasons or for receiving non-protocol anti-tumor therapy prior to disease progression. The proportion of subjects censored was similar among treatment arms. A sensitivity analysis of PFS whereby subjects who received non-protocol anti-tumor therapy were considered to have progressed showed that the FOLFOX4 + bevacizumab resulted in a statistically significant longer period of PFS.

The objective response rate was significantly higher ($p < 0.0001$) in the FOLFOX4 + bevacizumab arm (22.2%) than in the FOLFOX4 arm (8.6%). Almost all of the objective responses reported were PRs with only 0.7% complete responses in the FOLFOX4 arm and 1.7% complete responses in the FOFOX4 + bevacizumab arm. The determination of duration of objective response was based on a non-randomized subset of patients, and therefore formal hypothesis testing was not performed. However, treatment arms were compared for descriptive purposes. The duration of response was approximately 6 months for both treatment arms.

1.3.3 Safety

The Safety data collected during the conduct of Study E3200 was based on adverse events that were considered by the investigator to be related to protocol therapy. Events unlikely to be related to protocol therapy, but not able to be ruled out, were not reported. Because therapy assignment was open-label, the criteria applied by the investigator in the reporting of adverse events could have varied across treatment arms based on the investigator's determination of the attribution of the event to the specific treatment arm. Toxicity data was collected on the E3200 toxicity case report form.

The onset dates of adverse events were not collected, instead the reporting period (ranging from 1-3 months) during which the events occurred were collected on the toxicity form. Adverse events that led to the discontinuation or reduction in the dose of bevacizumab were not collected during the conduct of the study, but instead the Applicant attempted to retrospectively collect the adverse event data associated with bevacizumab dose modifications. Approximately 15% of the bevacizumab dose modification forms were not able to be retrospectively collected. In addition to the E3200 toxicity case report form, toxicity data was collected through the AdEEERs expedited reporting system, however, the reporting requirements for AdEERS varied by treatment arm and changed over time during the conduct of the study. The Applicant states in the submission the following regarding adverse events reported in an expedited fashion: "*Since the criteria for expedited reporting of adverse events were different in each treatment arm, comparisons of the incidence of adverse events between treatment arms that use expedited report event data must be interpreted with caution.*"

1.3.4 Dosing Regimen and Administration

The Avastin Package Insert recommended dose for first-line treatment of advanced or metastatic CRC is 5 mg/kg administered IV every two weeks in combination with 5-FU based chemotherapy. The E3200 study employed a dose of 10 mg/kg administered every two weeks for second-line advanced or metastatic CRC.

1.3.6 Special Populations

Elderly Subjects ≥ 65 years of age exhibited a similar treatment effect from the addition of bevacizumab to FOLFOX4 chemotherapy in prolonging the duration of survival as those subjects less than 65 years of age. The adverse events in Table 1 Adverse Events with an Increased Incidence in Subjects 65 Years of age and Older occurred at a higher frequency and relative risk in the FOLFOX4 + bevacizumab arm compared to the FOFOX4 alone arm in patients ≥ 65 years of age.

Table 1 Adverse Events with an Increased Incidence in Subjects 65 Years of age and Older

Adverse events with an increased incidence in subjects ≥ 65 years of age

Toxicity fold increase {(65-74)/< 65}	NCI-CTC Grade	< 65 (n=355)		≥ 65-74 (n=147)		≥ 74 (n=69)	
		FOLFOX4 (n=179)	FOLFOX4/BV (n=176)	FOLFOX4 (n=78)	FOLFOX4/BV (n=69)	FOLFOX4 (n=28)	FOLFOX4/BV (n=41)
Nausea {2.2}	3	9 (5.0%)	18 (10.2%)	2 (2.6%)	8 (11.6%)	1 (3.6%	5 (12.2%)
Emesis {4.7}	3-4	6 (3.4%)	14 (8.0%)	1 (1.3%)	10 (14.5%)	2 (7.1%)	5 (12.2%)
Ileus {7.2}	3	1 (0.6%)	1 (0.6%)	0 (0.0%)	5 (7.2%)	0 (0.0%)	2 (4.9%)
Fatigue {1.4}	3-4	20 (11.2%)	25 (14.2%)	12 (15.4%)	19 (27.5%)	5 (17.9%)	9 (22.0%)

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.

2.2 Currently Available Treatment for Indications

Irinotecan (Camptosar, CPT-11), oxaliplatin (Eloxatin), and cetuximab (Erbitux) are approved for use in patients with previously treated metastatic CRC.

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 of 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. Bevacizumab is currently marketed in the U.S. under the trade name Avastin by Genentech.

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, proteinuria, and arterial thromboses.

2.5 Presubmission Regulatory Activity

Study E3200 was conducted by ECOG under the NCI's IND application (BB-IND 7921). The protocol was first submitted to the IND July 25, 2001 and activated on October 30, 2001. The first four of eight total revisions to the protocol were submitted on September 28, and December 7, 2001, and August 22 and September 13, 2002. At that time the FDA responded to ECOG with a detailed letter outlining the deficiencies of the study. Please see Appendix 3 for a compilation of correspondence and meeting minutes between the FDA and ECOG/Genentech regarding the deficiencies of study E3200. 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.*
>
> *We have reviewed this protocol with respect to its ability to provide definitive conclusions as to the use of Bevacizumab in combination with oxaliplatin, 5-fluorouracil, and leucovorin. In its present form, study E3200 is inadequate in design to serve as one of several studies intended to support licensure or a new indication for the treatment of metastatic colorectal cancer. We have the following comments regarding deficiencies in study design that preclude use of the study results for this purpose:...*

Representatives of Genentech, NCI, and ECOG met with FDA on 23 March 2004 to address changes requested by FDA to Genentech's Statistical Analysis Plan (SAP). Although Genentech did modify the SAP that was to be used for the final efficacy analysis, ECOG did not change various aspects of the conduct of the study as requested. For example, the FDA specifically requested that serum chemistries and blood pressure measurements be obtained and recorded. The E3200 study did not collect this information, despite the known hypertensive side effects of bevacizumab. The deficiencies in study conduct are highlighted by the observation that the E3200 study did not collect in a prospective fashion bevacizumab dose modification or discontinuation data, or the toxicities associated with the need for dose modification, and instead retrospectively collected this data in an incomplete, and in some cases inaccurate fashion.

A revised SAP was submitted on 14 April 2004, prior to the DMC's first planned efficacy analysis. At the second planned interim efficacy analysis, the DMC determined that the analysis of the primary endpoint of survival met the pre-specified criteria for statistical significance for the comparison of FOLFOX4 + bevacizumab versus FOLFOX4.

Genentech and the FDA agreed during a March 10, 2005 Type B pre-sBLA meeting that the sBLA would contain specific review data. Genentech provided a revised proposal for the contents of the sBLA on July 1, 2005 that differed substantially from that agreed to during the March 10, 2005 teleconference. A statement contained in the July 1, 2005 submission stating that Genentech will *attempt* to identify the adverse event/toxicity that led to study discontinuation and that no source data verification will be performed, again highlight the deficiencies in the conduct of the E3200 study.

The FDA was notified by Genentech during an October 5, 2005 meeting regarding a number of upcoming Genentech supplements that the contents of this sBLA application would again be

different from the most recently proposed contents. The FDA responded that the wide scope of the October 5, 2005 meeting would not allow comment on individual applications and that the changes proposed by Genentech would be review issues.

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 ECOG-sponsored, randomized, three arm, active-controlled clinical trial conducted in the USA (Study E3200).

4.3 Review Strategy

The review consisted of analysis of data from study E3200.

4.4 Data Quality and Integrity

Genentech did not audit the E3200 study. 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 stated the following during the April 7, 2004 meeting involving Genentech, CTEP, ECOG and FDA:

> *Regarding verification of patient eligibility, ECOG stated that they normally audit 10% of the study sites. For study E3200, 17% of the study sites have been audited; the auditing process includes verification of patient eligibility. Regarding site audits, ECOG audits a site every 3 years, therefore, all sites participating in study E3200 were audited at least once during the conduct of the study, however, because the audits are of study sites, not of specific protocols, the level of auditing of patients enrolled in a specific protocol is unknown.*

Additionally, NCI/CTEP stated during a meeting held on September 16, 2004 that the clinical site audits are to fragmentary to provide assurance of adherence to Good Clinical Practices and/or study conduct.

The quality of adverse event data is questionable, as both ECOG and CTEP could independently alter the adverse event data based on queries to the individual sites and were not required to inform the other party. There is no electronic record of the rationale for changes made to an AdEERS report by NCI/CTEP, either within the report or elsewhere. The reconciliation performed by ECOG between the AdEERS data base and the ECOG clinical data base (Toxicity Forms) is conducted independently and often prior to the NCI/CTEP review. Genentech states that they will not attempt to perform reconciliation between the ECOG clinical and NCI/CTEP AdEERS data bases. The following statement by the Applicant characterizes the lack of thoroughness in the acquisition of safety data in Study E3200:

> *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.

Although the DSI field inspector observed no discrepancies with respect to the efficacy data at both clinical sites inspected, one of the sites was noted to have a number of deficiencies relating to study conduct. The deficiencies, as listed below, are likely related to the inadequate study monitoring and auditing procedures employed by ECOG. The final conclusion of the field inspector was that the data from Dr. Lilenbaum's site, associated with protocol E3200, submitted to the agency in support of efficacy supplement BLA 125085\74, is reliable.

Observations from the DSI inspection

Observation 1. An investigation was not conducted in accordance with the investigational plan.

a. According to the Protocol Transmittal Form, dated 12/5/01, submitted to the Mt. Sinai Medical Center IRB by the initial Clinical Investigator, Dr. Davila, "Following approval of the informed consent document, an accurate translation of the approved consent document must be submitted to the IRB. If a non-English speaking subject is unexpectedly encountered, investigators must rely on an oral translation. In this case, a 'short form' written consent document in the language the subject understands must be used to document that the elements of informed consent as required by 21 CFR 50 and 46 CFR 46 were translated and presented orally." The Protocol Transmittal Form clearly indicated that the investigator expected Spanish speakers to be candidate subjects in the study, E3200. However, the entire consent form was never translated into Spanish nor forwarded to the local IRB for approval. The IRB did approve a Spanish language "short form" for use along with a Spanish speaking translator to support oral consent. This short form was an addendum to the English ICD, provided for signature of the subject and stated essentially in written Spanish that the subject understood the contents of the English ICD on the study presented to them orally. The following subjects were consented using the above described, non-protocol directed, consenting procedures: 33003, 33035, 33124, 33181.
b. With respect to subject 33124 the following protocol-required tests were not done at the C7 study visit/treatment interval (2/20/03); SGOT, SGPT, alkaline phosphatase, and bilirubin.

Observation 2. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

a. The E3200 Treatment Summary Form for subject 33124 states that the treatment was ended due to, "tx regimen found to be inferior as per ECOG." In contrast, Dr. Lilenbaum's Consultation Report dated 9/17/03 states that, "the treatment was halted because of progressive proteinuria."
b. Subject 33124 was to have been dose reduced at the C7 cycle on 2/20/03 from 10 mg/kg to 5 mg/kg in response to a 24 hour protein result of 1,110 mg on 2/10/03. The full dose was given in error. However, the E3200 Treatment Summary Form dated 3/17/03 states that dose modifications or additions/omissions to protocol treatment were initiated as planned.
c. Scheduled treatment on 3/20/02 for subject 33003 was held until 3/27/02 without documented justification since there were no protocol defined toxicities requiring

that the treatment be held. This deviation was not documented in the E3200 Treatment Summary Form.

d. On 4/24/03 subject 33202 reported infusion pump leakage during treatment. The volume of drug "not administered" was not estimated nor was the incident reported in the E3200 Treatment Summary Form.

Observation 3. Failure to report promptly to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug.

a. The protocol requires reporting within 7 days of grade 3 unrelated or unlikely adverse events if subject is hospitalized.
   i. Subject 33084 experienced an infection with grade 3 neutropenia from 10/17/02 to 10/20/02, however, the NCI Adverse Event Expedited Report was not submitted until 12/26/02.
   ii. Subject 33035 experienced a grade 4 bowel obstruction with a start date of 3/11/02. The Adverse Event Report was prepared on11/11/02. [Observation made Post-Inspection.]

Observation 4. Investigational drug disposition records are not adequate with respect to use by subjects.

a. The study drug, Bevacizumab required storage at temperatures of 2-8 degrees Celsius [35.6 – 46.4 degrees Fahrenheit]. Review of main pharmacy temperature monitoring records specific to the refrigerator holding the study drug show sporadic storage temperatures of 47 degrees Fahrenheit and above. Sample temperature deviations are provided below:
   i. 12/16/01 to 12/19/01 temperature logs showed temperature ranging between 47 and 49 degrees Fahrenheit.
   ii. 2/20/02 to 2/21/02 temperature logs showed temperature ranging between 47 and 48 degrees Fahrenheit.
   iii. No temperature records were available from 3/2/02 to the end of patient treatment in 2003.

b. With respect to subject 33118 medication administration records shows the administration of Bevacizumab at 700 mg/sodium chloride 0.9% diluent with a total volume of 30 mL on both 2/19/03 and 3/5/03. Seven 4 mL vials (bevacizumab 25 mg/mL) for each drug administration were dispensed from the same lot, R9812A1. Therefore the drug volume for each dose would be 28 mL total volume. Other medication records for subject 33118 show either a 100 mL total volume of dosed material (assumed study drug, neat, plus saline diluent, as per protocol) or just the saline volume alone. It is not clear from these records why there are volume dosing discrepancies.

c. With respect to study subject 33150, study drug administration shows a volume of 40 cc for bevacizumab, and a total drug dose of 960 mg. However, the lot used for source material was packaged as 10mg/mL, therefore the volume of study drug alone should have been 96 cc not 40 cc.

4.5 Compliance with Good Clinical Practices

The Applicant states the study 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, during a September 16, 2004 discussion with FDA, the Sponsor of the Study E3200, CTEP,

stated that the clinical site audits employed by CTEP are too fragmentary to provide assurance of adherence to Good Clinical Practices and/or study conduct.

4.6 Financial Disclosures

Financial disclosure forms are available for only 70% of the investigators (154 of 221) during the period of time from study initiation to March 2002. The Applicant attempted to contact investigators by mail on two occasions to obtain financial disclosure information for this time period. None of the 154 respondents reported a disclosure for the time period of October 2001 to March 2002. Financial information is available for 447 of 463 investigators post March 2002. Nine investigators (1.9%) reported a disclosure during this time period, five of the disclosures related to equity investments worth > 50,000 dollars.

The Applicant 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 5 months of the study; however, in this reviewer's opinion, it does not appear that significant bias was introduced into the final results or ultimate conclusion drawn from the trial by financial conflicts of interest.

5 CLINICAL PHARMACOLOGY

Pharmacokinetic and pharmacodynamic studies were not conducted during this clinical study.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The current indication of Avastin is as follows: *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.*

Genentech proposes to revise the Indications section to the following:———————

b(4)

Reviewer comment: The following change to the Indications Section of the Package Insert is warranted by the clinical data reviewed in Study E3200: *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.*

6.1.1 Methods

The study report contained in this submission was reviewed for efficacy. In study E3200, clinical efficacy in the primary endpoint of duration of survival was compared between FOLFOX and FOLFOX + bevacizumab treatment groups. The components of 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 also performed. The FDA statistical reviewer confirmed the primary efficacy analyses.

6.1.2 General Discussion of Endpoints

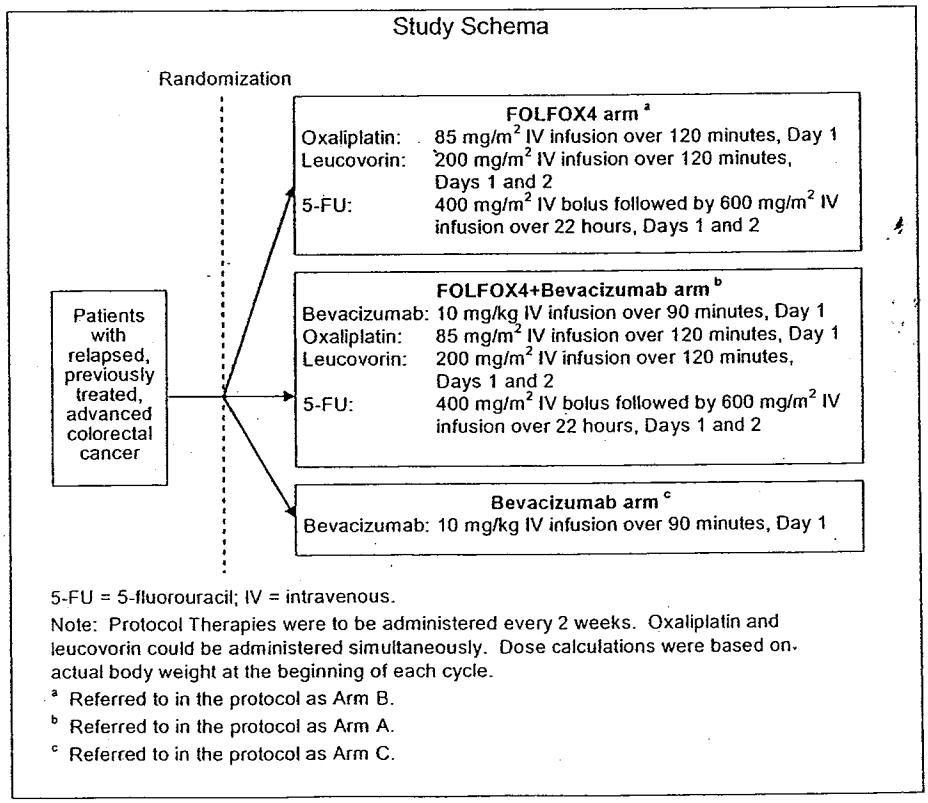
The primary efficacy endpoint for Study E3200 was duration of survival. The use of the primary endpoint in this study was acceptable. The Genentech statistical analysis plan included progression-free survival, objective response, and duration of objective response as secondary efficacy endpoints. The analysis of study data regarding the primary endpoint in this submission

was adequate to evaluate the relative efficacy of FOLFOX4 + bevacizumab compared to FOLFOX4 alone in prolonging the duration of clinically meaningful survival. Although the analysis of the study data regarding the secondary endpoints of objective response rate and progression free survival support the primary endpoint, these results are less robust as the study was not blinded and did not employ prespecified imaging acquisition parameters or centralized blinded review of source imaging data.

6.1.3 Study Design

Study E3200 was an open label, three arm, randomized 1:1:1, phase 3, multicenter, active-controlled trial to evaluate the efficacy and safety of FOLFOX4 versus FOLFOX4 + bevacizumab versus bevacizumab monotherapy in subjects with recurrent, advanced, or metastatic CRC who had previously received a fluoropyrimidine- and an irinotecan-based regimen. The study was conducted by the Eastern Cooperative Oncology Group (ECOG) and carried out at 220 sites in the United States. Patients could be enrolled on study through participating ECOG institutions and also via the Expanded Participation Program (EPP). The EPP was implemented by CTEP to allow for greater patient and non-cooperative group physician access to CTEP sponsored Trials. The study was conducted from Nov 13, 2001 to August 1, 2005 (date of ECOG data base transfer). The first subject was randomized on November 13, 2001 and the last subject was randomized on November 23, 2003. The bevacizumab monotherapy arm was closed to further enrollment on March 11, 2003, based on a review of early efficacy results by the DMC. After the discontinuation of the bevacizumab monotherapy arm, subjects were randomized in a 1:1 ratio between the FOLFOX4 and FOLFOX4 + bevacizumab arms. The following outline and schematic in Figure 1 summarize the E3200 Study design:

Figure 1 E3200 Study Schematic



Objectives

Primary:

- To evaluate the efficacy of bevacizumab when combined with FOLFOX4 versus FOLFOX4 alone in patients with advanced colorectal cancer who have failed therapy with irinotecan and 5-fluorouracil, as measured by duration of survival
- To evaluate the safety of bevacizumab when combined with FOLFOX4 versus FOLFOX4 alone in patients with advanced colorectal cancer who have failed therapy with irinotecan and 5-fluorouracil

Secondary:

- To evaluate the efficacy of bevacizumab when combined with FOLFOX4 versus FOLFOX4 alone in patients with advanced colorectal cancer who have failed therapy with irinotecan and 5-fluorouracil, as measured by progression-free survival, objective response, and duration of objective response.

Study Population

Inclusion Criteria

- Measurable, histologically confirmed, advanced or metastatic adenocarcinoma of the colon and rectum documented within 4 weeks prior to randomization.
- Prior treatment with a fluoropyrimidine-based regimen and an irinotecan-based regimen, either alone or in combination, for advanced disease and recovery from any treatment-related toxicities
    - History of relapse within 6 months of concluding adjuvant therapy with 5-FU and subsequent progression following single-agent irinotecan treatment was permitted.
    - History of relapse within 6 months of concluding adjuvant therapy with 5-FU in combination with irinotecan was permitted.
- Adequate renal function as demonstrated by serum creatinine ≤ 1.5 times the upper limit of normal (ULN) and proteinuria $< 1+$ based on urine dipstick within 4 weeks prior to randomization
    - If the urine dipstick revealed 1 + proteinuria, a 24-hour urine test had to demonstrate < 500 mg of protein.
    - Proteinuria was allowed if it was considered to be related to the use of ureteral stents and was not related to nephropathy.
- Adequate hepatic function as demonstrated by bilirubin $\leq 1.5 \times$ ULN and SGOT $\leq 5 \times$ ULN within 4 weeks prior to randomization
- Absolute neutrophil count $\geq$ 1,500/mm3 and platelet count $\geq$ 100,000/mm3 within 4 weeks prior to randomization
- International normalized ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) less than or equal to the institutional ULN (criterion changed PTT from within normal limits to less than or equal to the institutional ULN
- ECOG performance status of 0–2
- Age $\geq$ 18 years

- Use of accepted and effective method of contraception (e.g., hormonal or barrier methods, or abstinence) prior to study entry and for the duration of the study (women of childbearing potential and sexually active men only)

Exclusion Criteria

- Prior treatment with oxaliplatin or bevacizumab
- Radiotherapy treatment within 2 weeks prior to randomization
- Subjects must have recovered from any remaining toxicities related to radiotherapy.
- History of thrombotic or hemorrhagic disorders
- Use of therapeutic anticoagulation therapy
- Prophylactic anticoagulation for venous access devices was allowed provided the activity of the agent was reflected in INR or PTT measurements, and resulted in an INR ≤ 1.5 and PTT less than or equal to the institutional ULN.
- Pregnant or lactating
- Known brain metastases
- History of hypertension, unless blood pressure is well controlled (< 150/100 mmHg) on a stable regimen of antihypertensive therapy
- Major surgical procedure within 28 days prior to randomization
- Use of aspirin on a regular basis (> 325 mg/day) within 10 days prior to randomization
- Use of antiplatelet agents (specifically, dipyridamole, ticlopidine, clopidogrel, or cilostazol)
- Serious, non-healing wound, ulcer, or bone fracture
- History of myocardial infarction, uncontrolled congestive heart failure, or unstable angina within 3 months prior to randomization

Treatment Plan

- Protocol therapy was given in repeating 2-week cycles.
- Treatment was to be continued until disease progression, except that treatment was discontinued for patients who either achieved a partial response and underwent surgical resection of all existing disease or achieved a complete response and completed up to two additional cycles of treatment.
- There was no limit on the maximum number of cycles of protocol therapy.

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 5 mg/kg. If a second Grade 2 or greater event occurred, bevacizumab was to be permanently discontinued.
        - For a Grade 3 or 4 event, bevacizumab was to be permanently discontinued.
    - 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 < 500 mg, bevacizumab was to be resumed at 10 mg/kg (i.e., no change)
  - If the 24-hour protein measurement was ≥ 500 mg but ≤ 2 g, bevacizumab was to be resumed at 5 mg/kg
  - If the 24-hour protein measurement was > 2 g, bevacizumab was to be held until the 24-hour protein measurement resolved to ≤ 2 g; bevacizumab was then to be resumed at 5 mg/kg.
- After a dose reduction to 5 mg/kg, if a subsequent urine dipstick protein result was greater than the dipstick value that resulted in the dose reduction, bevacizumab was to be held and a 24-hour urine collection for protein measurement was to be performed.
  - If the result of the 24-hour protein measurement was < 0.5 g, bevacizumab was to be resumed at 5 mg/kg.
  - If the result of the 24-hour protein measurement was ≥ 0.5 g, bevacizumab was to be permanently discontinued.

- 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 ≤ 1 and then resumed at 5 mg/kg.
  - If a Grade 3 or 4 event occurred after dose reduction, bevacizumab was to be permanently discontinued.
- Coagulopathy
  - For a Grade 2 event, bevacizumab was to be reduced to 5 mg/kg.
  - For a Grade 3 or 4 event, bevacizumab was to be permanently discontinued.
  - In addition, bevacizumab was to be permanently discontinued in any patient requiring therapeutic anticoagulation.
- Hypertension
  - For a Grade 2 event, bevacizumab was to be reduced to 5 mg/kg.
  - For a Grade 3 or 4 event, bevacizumab was to be permanently is continued.
- Arterial thromboembolic events
  - For a Grade 2 event not present at baseline, or any Grade 3 or 4 event, bevacizumab was to be permanently discontinued.

- Patients treated with FOLFOX4 + bevacizumab who required discontinuation of bevacizumab treatment could continue to receive chemotherapy.
- Patients treated with FOLFOX4 + bevacizumab who required discontinuation of both oxaliplatin and 5-FU treatment could continue to receive 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 8 weeks.

  - Subjects who discontinued protocol therapy prior to progression continued to be evaluated for tumor response until disease progression; however, the protocol did not specify the frequency of tumor assessments after completion of protocol therapy.
- 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 collected while every 3 months on protocol therapy under the original protocol.
- Following Amendment 2, effective October 2002, the frequency of adverse event collection changed to monthly for the first six treatment cycles (12 weeks), and every 3 months thereafter.
- The onset date of the adverse event was not collected, but instead the reporting period ranging from 1 to 3 months during which the adverse event occurred was collected.
- Only Grade 4 and 5 hematologic and Grade 3-5 non-hematologic adverse events considered by the investigator to be related to protocol therapy were required to be reported.
- 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.
- Following discontinuation of protocol therapy, NCI-CTC Grade $\geq$ 3 adverse events not previously reported for a patient were to be collected until disease progression or the start of non-protocol therapy, whichever occurred first.
- Adverse events that required expedited reporting were reported to NCI's Adverse Event Expedited Reporting System (NCI AdEERS) as specified in the protocol. AdEERS reporting requirements differed between treatment arms and changed during the course of the study as a result of protocol amendments and changes to the Agent Specific Adverse Event List (ASEAL).
  - Grade 3 expected events (except for hemorrhage requiring transfusion) and that did not result in hospitalization or prolongation of existing hospitalization were not reported through AdEERS. Expectedness was based on the ASAEL that included overlapping toxicities between oxaliplatin and bevacizumab and the ASAEL changed over time. The adverse event reporting section of the protocol included the following instruction: *Because of ongoing changes to the ASAEL, please refer to the Adverse Event-AdEERS link on the ECOG webpage (www.ecog.org.) for the most up-to-date version.*
  - The Applicant specifically notes the limitations of the AdEERS reporting system and states that since the criteria for expedited reporting of adverse events were different in each treatment arm, comparisons of the incidence of adverse events between treatment arms that use expedited report event data must be interpreted with caution.
- An unsuccessful attempt was made to collect adverse events that led to bevacizumab dose reduction or discontinuation. This attempt to collect data was performed in a retrospective manner for patients in the FOLFOX4 + bevacizumab and bevacizumab monotherapy arms

using the E3200 Bevacizumab Dose Modification Form. The retrospective collection of data was incomplete and inaccurate.

- The Applicant notes multiple limitations of the ECOG narratives and states the following in the submission:

  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

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.
  - Duration of survival was formally compared between the FOLFOX4 + bevacizumab and FOLFOX4 arms using the two-sided stratified log-rank test and are also presented using Kaplan-Meier methodology.
  - The hazard ratio for death on the FOLFOX4 + bevacizumab arm relative to the FOLFOX4 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 $\alpha = 0.0167$ (two-sided). To control the Type I error rate for the primary endpoint of duration of survival, accounting for two formal efficacy interim analyses, the Lan and DeMets implementation of the O'Brien-Fleming a-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
    - Race (White, non-White)
    - Number of involved sites (1, > 1)
    - Baseline CEA value (greater than ULN, less than or equal to ULN)
    - 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 consist 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. Tumor assessments performed more than 60 days following

the date of last protocol therapy or after the start of non-protocol therapy (when available) were not considered in the analyses of PFS

- 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. The test was performed at the two-sided 0.0167 level of significance. 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 paraphrased delineation of substantive changes for each protocol amendment as provided by the sponsor in the CSR.

6.1.4 Efficacy Findings

6.1.4.1 Study Conduct

Eight hundred and twenty nine subjects were randomized on this study: 292 patients to FOLFOX4 arm, 293 patients to FOLFOX4 + bevacizumab arm, and 244 patients to bevacizumab monotherapy arm. Randomization was conducted in a 1:1:1 ratio from November 13, 2001 until March 11, 2003. On March 11, 2003 the bevacizumab monotherapy arm was closed to further enrollment based on a review of early results by the DMC. Overall, 806 patients (97.2%) received protocol therapy and no patients remain on protocol therapy. A total of 220 centers randomized subjects into this study. Enrollment by center ranged from 1 to 24 patients. For a summary of subject disposition see Table 2: Subject Disposition (reproduced from the CSR section 10.1, page 59).

Table 2: Subject Disposition

Reason Provided by Investigator	FOLFOX4 (n=292)	FOLFOX4 + Bevacizumab (n=293)	Bevacizumab (n=244)	Total (n=829)
Treated	285 (97.6%)	287 (98.0%)	234 (95.9%)	806 (97.2%)
Continuing protocol therapy	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.1%) [b]
Protocol therapy ended	285 (97.6%)	287 (98.0%)	233 (95.5%)	805 (97.1%)
Treatment completed (PR with resection or CR) [a]	3 (1.0%)	3 (1.0%)	1 (0.4%)	7 (0.8%)
Disease progression/relapse during active treatment	147 (50.3%)	141 (48.1%)	159 (65.2%)	447 (53.9%)
Toxicity/side effects/complications	69 (23.6%)	66 (22.5%)	28 (11.5%)	163 (19.7%)
Death on study	7 (2.4%)	12 (4.1%)	6 (2.5%)	25 (3.0%)
Patient withdrawal or refusal	21 (7.2%)	25 (8.5%)	5 (2.0%)	51 (6.2%)
Alternative therapy	4 (1.4%)	5 (1.7%)	2 (0.8%)	11 (1.3%)
Other complicating disease	3 (1.0%)	4 (1.4%)	2 (0.8%)	9 (1.1%)
Other	30 (10.3%)	31 (10.6%)	29 (11.9%)	90 (10.9%)
Not stated	1 (0.3%)	0 (0.0%)	1 (0.4%)	2 (0.2%)
Not treated	7 (2.4%)	6 (2.0%)	10 (4.1%)	23 (2.8%)
Died	0 (0.0%)	1 (0.3%)	2 (0.8%)	3 (0.4%)
Ineligible	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Refused treatment	5 (1.7%)	2 (0.7%)	5 (2.0%)	12 (1.4%)
Other	1 (0.3%)	3 (1.0%)	3 (1.2%)	7 (0.8%)

CR=complete response; FOLFOX4=oxaliplatin/5-fluorouracil/leucovorin; PR=partial response.
Note: Percentages were computed relative to the number of randomized patients. Enrollment in the bevacizumab monotherapy arm was closed 1 month prior to cessation of enrollment in the principal arms. "Reason protocol therapy ended" was not provided for 1 patient in the FOLFOX4 arm (32221) and 1 patient in the bevacizumab monotherapy arm (33002).

[a] Per protocol, treatment was considered completed for patients who either achieved a partial response and underwent surgical resection of all existing disease or achieved a complete response and completed up to two additional cycles of treatment.

[b] One patient is shown as continuing protocol therapy, as indicated by the lack of the therapy end date; however, this patient has died, and therefore no patients remain on protocol therapy.

As reported by the Applicant, protocol deviations were not completely assessed. The reason stated by Genentech for the incomplete information on protocol deviations is lack of assessment by ECOG. Among treated patients, ECOG assessed 710 patients for incorrect treatment arm, 713 patients for treatment before registration, 652 patients for stratification errors, and 567 patients for other deviations. Forty-one 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 was administration of non-protocol anti-tumor therapy prior to progression. The non-protocol anti-tumor therapy administered prior to disease progression consisted primarily of chemotherapy and was used in a similar proportion of subjects on the FOLFOX4 and FOLFOX4 + bevacizumab arms, 13.7% and 13.2% respectively.

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. However, the primary documented protocol deviation of non-protocol anti-tumor therapy administered prior to disease progression was balanced between the two compared treatment arms, and therefore is unlikely to have affected the study results. In addition, the use of non-protocol anti-tumor therapy would be expected to confound only the secondary endpoints of progression free survival (PFS) and objective response rate (ORR). Two sensitivity analyses provided by the Applicant on the effect of non-protocol anti-tumor therapy on the PFS endpoint and one performed by FDA did not change the conclusion of the analysis of the study results.*

6.1.4.2 Study Demographics.

The baseline characteristics of the study subjects are shown in Tables 3-6 (Table 3: Subject Demographics Table 4: Prior Cancer Treatment, Table 5: Tumor Site Involvement Table 6: Disease Status) (Reproduced from Tables 6-9 of the CSR). There were no clinically relevant baseline imbalances between study arms. All of the subjects had colorectal cancer. It is not possible from the case report forms or study data to identify subjects that entered study following adjuvant chemotherapy and subsequent relapse, however, approximately 12% of subjects had disease confined to the primary site or tumor bed, most likely representing a subset of subjects who relapsed following adjuvant chemotherapy. The remaining subjects had advanced or metastatic disease with a similar distribution of tumor site involvement between treatment groups. The incompletely evaluated eligibility forms document that approximately 3.5% of subjects received either combined or sequential adjuvant therapy with irinotecan and 5-FU prior to entering study. Ninety-three percent of subjects had tumor resection surgery, 26% had received radiotherapy, and 79% received adjuvant chemotherapy. The Applicant states that the ECOG "Eligibility Checklist" (data available for only 80% of subjects) was used to determine that 97% of subjects had received chemotherapy for advanced disease. The "Eligibility Checklist" primary data forms were not provided in the BLA supplement for review.

Table 3: Subject Demographics

	FOLFOX4 (n=292)	FOLFOX4 + Bevacizumab (n=293)	Bevacizumab (n=244)	Total (n=829)
Age (yr)				
n	292	292	244	828
Mean (SD)	60.3 (10.7)	61.3 (11.0)	59.4 (11.4)	60.4 (11.0)
Median	61	62	59	61
Range	25–84	21–85	23–82	21–85
Age category (yr)				
n	292	292	244	828
<40	4 (1.4%)	9 (3.1%)	13 (5.3%)	26 (3.1%)
40–64	182 (62.3%)	172 (58.9%)	141 (57.8%)	495 (59.8%)
≥65	106 (36.3%)	111 (38.0%)	90 (36.9%)	307 (37.1%)
Sex				
n	292	293	244	829
Female	115 (39.4%)	116 (39.6%)	99 (40.6%)	330 (39.8%)
Male	177 (60.6%)	177 (60.4%)	145 (59.4%)	499 (60.2%)
Race/ethnicity				
n	292	293	244	829
Black	20 (6.8%)	25 (8.5%)	21 (8.6%)	66 (8.0%)
Filipino	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Hawaiian	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Hispanic	7 (2.4%)	10 (3.4%)	8 (3.3%)	25 (3.0%)
Indian	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Native American	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Oriental	3 (1.0%)	1 (0.3%)	2 (0.8%)	6 (0.7%)
White	257 (88.0%)	256 (87.4%)	208 (85.2%)	721 (87.0%)
Other	1 (0.3%)	1 (0.3%)	1 (0.4%)	3 (0.4%)
Unknown	0 (0.0%)	0 (0.0%)	4 (1.6%)	4 (0.5%)

Table 4: Prior Cancer Treatment

	FOLFOX4 (n=292)	FOLFOX4 + Bevacizumab (n=293)	Bevacizumab (n=244)	Total (n=829)
Prior cancer treatment				
n	292	293	244	829
Any	288 (98.6%)	289 (98.6%)	240 (98.4%)	817 (98.6%)
Surgery	273 (93.5%)	266 (90.8%)	235 (96.3%)	774 (93.4%)
Adjuvant chemotherapy	232 (79.5%)	230 (78.5%)	198 (81.1%)	660 (79.6%)
Adjuvant immunotherapy	7 (2.4%)	1 (0.3%)	3 (1.2%)	11 (1.3%)
Radiotherapy	73 (25.0%)	77 (26.3%)	64 (26.2%)	214 (25.8%)
Prior treatment history for eligibility purposes				
n	235	235	194	664
Chemotherapy for advanced disease	223 (94.9%)	230 (97.9%)	188 (96.9%)	641 (96.5%)
Adjuvant 5-FU; single-agent irinotecan	8 (3.4%)	3 (1.3%)	6 (3.1%)	17 (2.6%)
Adjuvant 5-FU+irinotecan	4 (1.7%)	2 (0.9%)	0 (0.0%)	6 (0.9%)

Table 5: Tumor Site Involvement

	FOLFOX4 (n=292)	FOLFOX4 + Bevacizumab (n=293)	Bevacizumab (n=244)	Total (n=829)
Number of involved sites				
n	292	293	244	829
Mean (SD)	2.2 (1.1)	2.3 (1.2)	2.4 (1.1)	2.3 (1.1)
Median	2	2	2	2
Range	1–8	1–8	0–6	0–8
Number of involved sites category				
n	292	293	244	829
0	0 (0.0%)	0 (0.0%)	2 (0.8%)[a]	2 (0.2%)
1	88 (30.1%)	87 (29.7%)	54 (22.1%)	229 (27.6%)
>1	204 (69.9%)	206 (70.3%)	188 (77.0%)	598 (72.1%)
Sites of involvement				
n	292	293	242	827
Primary site or tumor bed	37 (12.7%)	35 (11.9%)	36 (14.9%)	108 (13.1%)
Regional lymph nodes	50 (17.1%)	43 (14.7%)	44 (18.2%)	137 (16.6%)
Distant lymph nodes	69 (23.6%)	62 (21.2%)	60 (24.8%)	191 (23.1%)
Lung	148 (50.7%)	164 (56.0%)	146 (60.3%)	458 (55.4%)
Liver	221 (75.7%)	214 (73.0%)	173 (71.5%)	608 (73.5%)
Other abdominal	69 (23.6%)	70 (23.9%)	53 (21.9%)	192 (23.2%)
Bone	17 (5.8%)	22 (7.5%)	19 (7.9%)	58 (7.0%)
Brain	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)
Distant skin/subcutaneous	3 (1.0%)	6 (2.0%)	4 (1.7%)	13 (1.6%)
Other	42 (14.4%)	44 (15.0%)	46 (19.0%)	132 (16.0%)
SLD of target lesions (cm)				
n	267	267	225	759
Mean (SD)	11.8 (7.7)	11.1 (8.1)	12.4 (9.7)	11.7 (8.5)
Median	10	9	10	10
Range	1–37	1–49	1–60	1–60

Table 6: Disease Status

	FOLFOX4 (n=292)	FOLFOX4 + Bevacizumab (n=293)	Bevacizumab (n=244)	Total (n=829)
ECOG performance status (baseline)				
n	291	293	244	828
0	148 (50.9%)	141 (48.1%)	118 (48.4%)	407 (49.2%)
1	126 (43.3%)	138 (47.1%)	107 (43.9%)	371 (44.8%)
2	17 (5.8%)	14 (4.8%)	19 (7.8%)	50 (6.0%)
ECOG performance status category (baseline)				
n	291	293	244	828
0	148 (50.9%)	141 (48.1%)	118 (48.4%)	407 (49.2%)
≥1	143 (49.1%)	152 (51.9%)	126 (51.6%)	421 (50.8%)
CEA (ng/mL)				
n	291	290	244	825
Mean (SD)	1018.6 (5124.3)	594.9 (3485.9)	596.1 (1510.7)	744.7 (3770.6)
Median	56	61	70	62
Range	0–56400	1–55770	1–12587	0–56400
CEA category (ng/mL)				
n	291	286	244	821
≤ULN	30 (10.3%)	26 (9.1%)	27 (11.1%)	83 (10.1%)
>ULN	261 (89.7%)	260 (90.9%)	217 (88.9%)	738 (89.9%)

In summary, precise characterization of tumor attributes and prior therapy received for subjects is not possible based on the CRF data supplied for review. Indeed, some subjects may have been enrolled on study after receiving only one- or a minimal number of- cycle(s) of a 5-FU/irinotecan based regimen. For the purposes of this review, it is assumed that the Cooperative Group

Investigator's assessment of eligibility criteria was done accurately, and that randomization of 829 subjects into the study resulted in an equal distribution of unknown protocol deviations into each arm.

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 duration of survival was increased from 10.8 months in the FOLFOX4 arm to 13.0 months in the FOFLFOX4 + bevacizumab arm with a p-value of 0.0012 { See Table 7: Duration of Survival (Randomized Subjects) Adapted from Table 11 of the CSR}. A sensitivity analysis in which subjects lost to follow-up were considered to have experienced death instead of being censored also showed that duration of survival improved in the FOLFOX + bevacizumab arm compared with the FOLFOX arm.

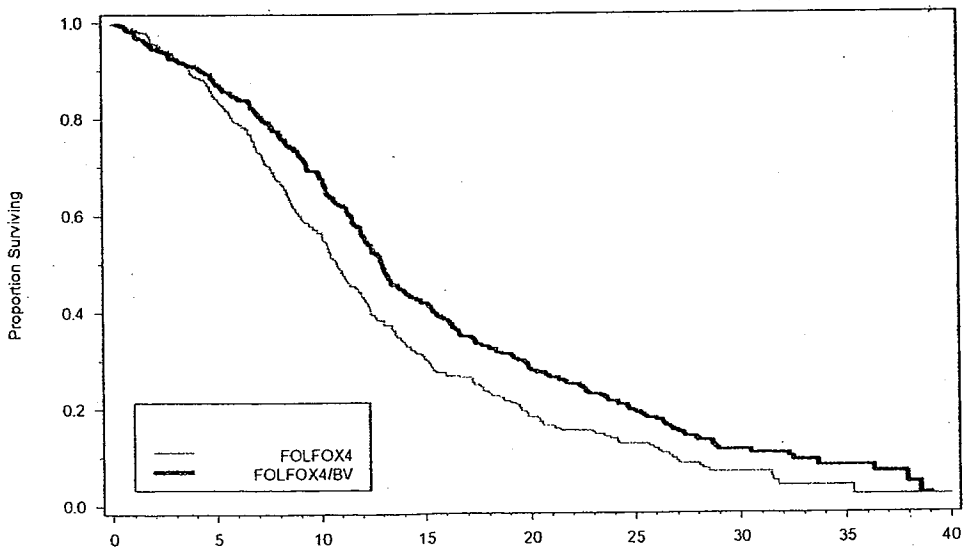
Table 7: Duration of Survival (Randomized Subjects)

	FOLFOX4 (n=292)	FOLFOX4 + Bevacizumab (n=293)
Subjects who died	265	260
Censored observations	27 (9.2%)	33 (11.3%)
Duration of survival (mo)		
Median	10.8	13.0
95% CI	(10.12, 11.86)	(12.09, 14.03)
Stratified analysis		
Hazard Ratio[a]	NA	0.751
95% CI	NA	(0.632, 0.893)
p-value (log-rank)	NA	0.0012

CI = confidence interval; NA= not applicable
[a] Relative to FOLFOX4. The strata are ECOG performance status (0, ≥1) and prior radiotherapy (yes, no).

Median follow-up for the surviving subjects was 25.0 months (FOLFOX4) and 28.9 months (FOLFOX4 + bevacizumab). 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 2 of the CSR.

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



Subset analyses based on demographic and baseline characteristics were conducted by the Applicant for the following variables: ECOG performance status at study entry (0, ≥ 1), prior radiotherapy (yes, no), age (< 40, 40–64, ≥ 65 years), sex, race (White, non-White), number of involved sites (1, > 1), baseline CEA value (less than or equal to ULN, greater than ULN), and baseline sum of longest diameters of all target lesions (less than median, greater than or equal to median). The results of the subset analyses for the primary efficacy endpoint of duration of survival were generally consistent with those for the randomized population as a whole. Some of the variables analyzed contained small numbers of subjects in a particular category and therefore were associated with wide 95% confidence intervals. The only variable that revealed a hazard ratio greater then 1, favoring the FOLFOX4 alone arm, was a carcinoembryonic antigen level less than the upper limit of normal (Hazard Ratio 1.11 {95%CI 0.66-2.03}).

Exposure data on the components and amounts of 5-FU, leucovorin, and oxaliplatin administered to subjects on the FOLFOX4 and the FOLFOX4 + bevacizumab arms were not collected in Study E3200. Adequate assessment for the possible confounding effects of unequal exposure to FOFLOX4 chemotherapy on the duration of survival between treatment arms cannot be performed. For the purposes of this review, it is assumed that because of the randomized study design and number of subjects accrued to each arm, any exposure bias would be minimized.

6.1.4.4 Secondary Analyses

The population analyzed for the secondary efficacy endpoints of progression-free survival (PFS) and objective response rate consisted of all subjects randomized to the 2 compared treatment arms. 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 PFS and OR data from study E3200 are less robust 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 a radiology review charter using an independent blinded review of the source tumor assessment images.
4. The study did not utilize a standard operating procedure for imaging acquisition and archiving.

PFS was defined as the time from randomization to disease progression or to death from any cause within 30 days following discontinuation of protocol therapy. Tumor assessments performed more than 60 days following the date of last protocol therapy or after the start of non-protocol therapy were not considered in the analyses of PFS.

A stratified analysis of PFS for all subjects randomized to the compared treatment arms revealed an increase in PFS among FOLFOX4 + bevacizumab subjects compared with FOLFOX4 subjects ($p < 0.0001$). Median PFS was 7.5 months in the FOLFOX4 + bevacizumab arm and 4.5 months in the FOLFOX4 arm. The stratified hazard ratio for disease progression or death for FOLFOX4 + bevacizumab relative to FOLFOX4 was 0.518 (95% CI: 0.42, 0.65) {See Table 9: Progression-Free Survival (Randomized Subjects) adapted from Table 13 of the CSR} Kaplan-Meier curves for PFS are shown in Figure 3: Kaplan-Meier Estimate of Progression-Free Survival (Randomized Subjects). An unusually large percentage of subjects were censored in the PFS analysis performed by the Applicant. Censoring was performed for subjects who came off therapy for toxicity reasons and had imaging assessments performed more than 60 days after having last received protocol therapy. Subjects were also censored at the time they began non-

protocol anti-tumor therapy. 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 (see Table 8: Worse case non-protocol anti-tumor therapy sensitivity analysis for PFS) whereby subjects 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. This worse case sensitivity analysis of PFS did not change the results of the study. Two additional analyses, one performed by the Applicant and one by FDA, on the frequency of imaging assessment by treatment arm did not reveal an ascertainment bias in the PFS data.

Table 8: Worse case non-protocol anti-tumor therapy sensitivity analysis for PFS

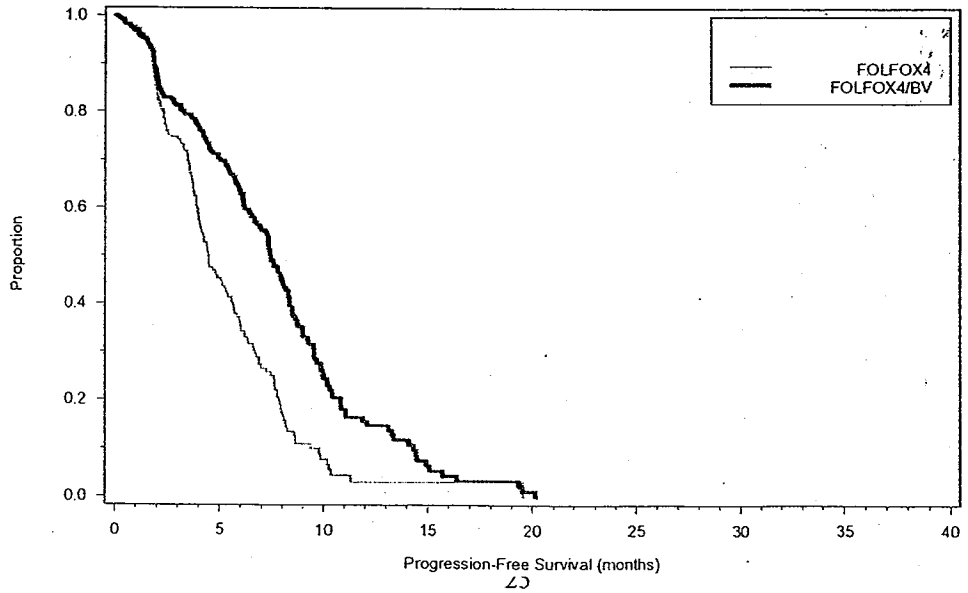
	FOLFOX4 (n=292)	FOLFOX4 + bevacizumab (n=293)
Median progression free survival (95% CI)	4.3(4.0, 4.6)	7.3(6.2, 7.6)
Hazard ratio (95% CI)		0.52(0.43, 0.63)

Table 9: Progression-Free Survival (Randomized Subjects)

	FOLFOX4 (n=292)	FOLFOX4 + bevacizumab (n=293)
Subjects with an event	179	177
Disease progression	169	160
Death	10	17
Censored observations	113	116
Progression-free survival		
Median	4.5	7.5
95% CI	(4.07, 5.26)	(6.77, 8.18)
Stratified analysis		
Hazard ratio[a]	NA	0.518
95% CI	NA	(0.416, 0.646)
p-value (log-rank)	NA	< 0.0001

CI = confidence interval; NA= not applicable
[a] Relative to FOLFOX4. The strata are ECOG performance status (0, ≥1) and prior radiotherapy (yes, no).

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



The objective response rate for randomized subjects was higher ($p < 0.0001$) in the FOLFOX4 + bevacizumab arm (22.2%) than in the FOLFOX4 arm (8.6%) {See Table 10: Objective Response (Randomized Subjects)}. The vast majority of objective responses reported were PRs. Eight (3.3%) partial responses were reported on the bevacizumab monotherapy arm. The median duration of objective response, approximately six months, was similar for both treatment arms.

Table 10: Objective Response (Randomized Subjects)

	FOLFOX4 (n=292)	FOLFOX4 + bevacizumab (n=293)
Objective response (%)	25 (8.6%)	65 (22.2%)
95% CI	(5.7%, 12.5%)	(17.6%, 27.5%)
p-value[a]	NA	< 0.0001
Best objective response		
Complete response	2 (0.7%)	5 (1.7%)
Partial response	23 (7.9%)	60 (20.5%)

Symptomatic deterioration without disease progression was recorded on the ECOG Follow-Up Disease Evaluation Form for 35 of 70 subjects (50%) on the FOLFOX4 arm (285) and 56 of 83 subjects (67.5%) on the FOLFOX4 + bevacizumab arm (287). The Applicant states that these results must be interpreted with caution as the assessment of symptomatic deterioration was made by the investigator, whereas tumor response and disease progression were assessed centrally by the E3200 Coordinating Center. This reviewer notes that tumor response and disease progression were also made by the investigator and only the numerical tumor measurements were reviewed centrally by ECOG.

Although Study E3200 met the primary endpoint of prolonging survival, the results of the analyses for progression-free survival and objective response were significantly less robust. 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 data acquisition parameters and evaluation criteria. Due to the nature and process of ECOG auditing of clinical studies, and the previously described confounding factors associated with the secondary endpoints of Study E3200, FDA requested 13 complete sets of films from 3 clinical sites on subjects with reported objective responses for a spot audit to assess the reliability of the data as provided in the CRTs. The FDA field inspector confirmed that all requested films at the Thomas Jefferson University site were available for review. In reply to this request, the Applicant requested that "*the FDA rely on the ECOG-reviewed investigator assessments of response and disease progression, which are based on the tumor measurements provided in this BLA supplement, rather than on a radiologic review of scans for certain patients.*" The reluctance or inability of the Sponsor to provide for spot review of the requested films and the fact that at least one of the three sites from which films were requested was documented by the field investigator as possessing the films on site, further compromises the agency's confidence in the radiology based secondary endpoints.

6.1.6 Efficacy Conclusions

The data reviewed in this submission from the randomized, multi-center trial, demonstrated that FOLFOX4 + bevacizumab, as compared to FOLFOX4 alone, prolonged the duration of survival by a clinically meaningful increment of 2.2 months in subjects with CRC who had previously

received 5-FU and irinotecan for advanced or metastatic disease or in subjects who recurred after adjuvant 5-FU and irinotecan based chemotherapy. The secondary endpoints of PFS and ORR support the primary efficacy endpoint.

7 INTEGRATED REVIEW OF SAFETY

The following discussions of adverse event data incidence rates are based on the following number of subjects per arm: FOFLOX4 = 285, FOLFOX4 + bevacizumab = 287, and Bevacizumab = 234.

7.1 Methods and Findings

The quality and reliability of the adverse event data collected in study E3200 is decreased compared to generally accepted FDA standards for initial BLA registration for the following reasons:

- Only Adverse events determined by the investigator to be possibly, probably, or definitely related to protocol therapy were collected on the E3200 Toxicity Form.
- Adverse event onset dates were not recorded, but instead the reporting period during which the adverse events occurred were documented. From activation of Study E3200 in October 2001 to October 16, 2002, the E3200 Toxicity Form was to be submitted every three months. Effective October 16, 2002 the Toxicity Form was to be submitted every month for the first 3 months of treatment and then every 3 months thereafter. 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 AdEERS reporting requirements were different by treatment arm and changed over time during the course of the study.
- Both ECOG and CTEP could independently alter the adverse event data based on queries to the individual sites and were not required to inform the other party.
- There is no electronic record of the rationale for changes made to an AdEERS report by NCI/CTEP, either within the report or elsewhere.
- The reconciliation performed by ECOG between the AdEERS data base and the ECOG clinical data base (Toxicity Forms) was conducted independently and often prior to the NCI/CTEP review.
- Genentech states that they would not attempt to perform reconciliation between the ECOG clinical and NCI/CTEP AdEERS data bases.
- The narratives are written using AdEERS derived language and data.
- Data indicating whether the bevacizumab dose was reduced or discontinued for toxicity were collected in a retrospective and incomplete fashion.
- The narratives for subjects taken off of study for toxicity reasons do not identify the toxicities responsible for discontinuation of protocol therapy.
    - A review of a random sample of narratives from 13 subjects identified as having received non-protocol anti-tumor therapy prior to disease progression revealed that 7 of the 13 narratives stated that the subject stopped protocol therapy because of unspecified toxicities.
    - The Applicant 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 CRT data bases provided for review do not identify toxicities that resulted in treatment discontinuation.
- Genentech states that since the criteria for expedited reporting of adverse events were different in each treatment arm, comparisons of the incidence of adverse events between treatment arms that use expedited report event data must be interpreted with caution.

In addition, the study did not capture vital sign data, therefore, correlation of blood pressure measurements with the onset and duration of hypertensive adverse events cannot be performed. The study also did not capture basic laboratory data such as electrolytes, urinalysis results or complete blood counts.

The E3200 study reporting requirements from protocol addendum number 2 are reproduced from the E3200 CSR in Figure 4: ECOG AE Reporting Requirements. For AdEERS reporting, Grade 4 or 5 adverse events were collected and recorded in a similar fashion across treatment arms regardless of expectedness or attribution. The collection and recording of grade 2-3 adverse events was filtered at the investigator level by "expectedness" and by attribution using the categories "possible", "probable" or "definite". Grade 2-3 expected events based on the AdEERS Agent Specific Adverse Event List (ASAEL) were not required to be collected. Table 11: Bevacizumab ASAEL and Table 12: Oxaliplatin ASAEL are derived from the NCI AdEERS Agent Specific Adverse Event List (ASAEL) in effect during protocol addendum 2. The ASAEL is a list of events that, because of human experience with the agent, should be considered expected events for adverse event expedited reporting purposes. The reporting requirements therefore were different between treatment arms based on ASAEL.

In addition, adverse events listed in the ASAEL that were common between agents would not be reported even if there was significant synergistic toxicity encountered with use of the combined agents. For example, hypertension is listed in the ASAEL for both oxaliplatin and bevacizumab, therefore grade 3 hypertensive events would not be reported in the FOLFOX4 arm or the FOLFOX4 + Bevacizumab arm, even if the combination of bevacizumab to oxaliplatin increased the incidence of grade 3 hypertension from 5% to 30%. The ASAEL does not address expected incidence rates of specific adverse events. Adverse events that were shared in common between oxaliplatin and bevacizumab in protocol addendum 2 are highlighted in grey in the ASAEL tables below. During the E3200 study the ASAEL list for agent specific expectedness and the ECOG reporting requirements changed over time during the conduct of the study, further confounding the use of AdEERS expedited reporting system for grade 2-3 adverse events, including some grade 4 events that would be considered SAEs. For example the FOLFOX4 + bevacizumab arm contained the following revision to the AdEERS reporting requirements in addendum 3:

d For study arm A, the adverse events listed below do **not** require expedited reporting via AdEERS, including hospitalization for these events:

- Grade 1-4 Stomatitis/pharyngitis
- Grade 1-4 Fever without neutropenia
- Grade 1-4 Infection without neutropenia
- Grade 1-4 Headache
- Grade 1-4 Thrombosis/Embolism

Some of the numerous changes in the AdEERS reporting requirements over time are compiled in Appendix 2.

Figure 4: ECOG AE Reporting Requirements

5.2 Adverse Event Reporting Requirements

5.21 EGOG Institutions

This study will utilize the CTC version 2.0 for toxicity and Adverse Event (AE) reporting. A copy of the CTC version 2.0 should be available at your institution. It can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0. Please refer to NCI Guidelines for Expedited Adverse Event Reporting Requirements for NCI Investigational Agents (http://ctep.cancer.gov/reporting/adeers/html).

5.211 The following events must be reported to ECOG, the NCI and your local IRB in the manner described below.

Arms: A, B, C
Investigational Agents: Bevacizumab, Oxaliplatin
Commercial Agents: 5-FU, Leucovorin

	Grade 2-3 Unexpected[1] With Attribution of Possible, Probable, or Definite[6]	Hospitalization[3]	Grade 4-5 Unexpected[1], Regardless of Attribution[5]	Grade 4-5 Expected[2], Regardless of Attribution[5]	Grade 3 or Higher Hemolysis With Any Grade Renal Failure	Grade 3-5 Hemorrhagic Event[7]
Call to NCI within 24 hours			X			X
Call to ECOG within 24 hours			X			X
Report[4] to ECOG within 10 working days	X	X	X	X	X	X
Notify local IRB within 10 working days	X	X	X	X		X

[1]An unexpected event for AdEERS reporting purposes is defined as one that is not listed on the NCI AdEERS Agent Specific Adverse Event List. This list is included in Appendix VIII of the protocol. To view the most up to date list, please go to the Adverse Event-AdEERS link on the ECOG webpage (www.ecog.org.)
[2]Grade 4 expected myelosuppression need not be reported, but those labs should be documented on the Toxicity Form.
[3]For hospitalizations: any event which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected, grade and attribution.
[4]Submitreport to ECOG using the *Adverse Event Expedited Report - Single Agent or Multiple Agents*, based on the number of agents in the patient's protocol-specific regimen. Reports must be submitted on-line using the AdEERS program found on the CTEP webpage (http://ctep.cancer.gov/reporting/adeers.html). ECOG will forward the AE reports on to all regulatory agencies (including NCI, FDA, and pharmaceutical company, if applicable).
[5]This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution; or any death attributed to the agent (possible, probable, or definite) regardless of the time frame.
[6]Events that are attributed to the commercial agents only need not be reported, but should be documented on the protocol-specific forms.
[7]Hemoptysis or Hemorrhage: Grade 3-requiring transfusion, Grade 4-catastrophic, requiring major non elective intervention, grade 5 - death.

Table 11: Bevacizumab ASAEL

Agent Specific Adverse Events Agent Name: BEVACIZUMAB

Category	Adverse Events	Other Specify	Comments
CARDIOVASCULAR (GENERAL)	Hypertension		
CARDIOVASCULAR (GENERAL)	Thrombosis/embolism		
CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10e9/L)		
CONSTITUTIONAL SYMPTOMS	Rigors, chills		

Agent Specific Adverse Events Agent Name: BEVACIZUMAB			
Category	Adverse Events	Other Specify	Comments
DERMATOLOGY/SKIN	Rash/desquamation		
GASTROINTESTINAL	Stomatitis/pharyngitis (oral/pharyngeal mucositis)		
HEMORRHAGE	CNS hemorrhage/bleeding		
HEMORRHAGE	Epistaxis		
HEMORRHAGE	Hematemesis		
HEMORRHAGE	Hemoptysis		
HEMORRHAGE	Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia		
INFECTION/FEBRILE NEUTROPENIA	Infection without neutropenia		
PAIN	Headache		
RENAL/GENITOURINARY	Proteinuria		

Table 12: Oxaliplatin ASAEL

Agent Specific Adverse Events Agent Name: OXALIPLATIN			
Category	Adverse Events	Other Specify	Comments
ALLERGY/IMMUNOLOGY	Allergic reaction/hypersensitivity (including drug fever)		
AUDITORY/HEARING	Inner ear/hearing		Hearing decreased (mild)
AUDITORY/HEARING	Middle ear/hearing		Ototoxicity (mild)
BLOOD/BONE MARROW	Hemoglobin		
BLOOD/BONE MARROW	Hemolysis (e.g., immune hemolytic anemia, drug related hemolysis, other)		
BLOOD/BONE MARROW	Leukocytes (total WBC)		
BLOOD/BONE MARROW	Neutrophils/granulocyteS (ANC/AGC)		
BLOOD/BONE MARROW	Platelets		
CARDIOVASCULAR (ARRHYTHMIA)	Sinus tachycardia		
CARDIOVASCULAR (ARRHYTHMIA)	Supraventricular arrhythmias (SVT /atrial fibrillation/flutter)		
CARDIOVASCULAR (ARRHYTHMIA)	Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia)		
CARDIOVASCULAR (GENERAL)	Edema		
CARDIOVASCULAR (GENERAL)	Hypertension		
CARDIOVASCULAR (GENERAL)	Phlebitis (superficial)		
CARDIOVASCULAR (GENERAL)	Thrombosis/embolism		Including pulmonary embolism
COAGULATION	DIC (disseminated intravascular coagulation)		
CONSTITUTIONAL SYMPTOMS	Fatigue (lethargy, malaise, asthenia)		
CONSTITUTIONAL SYMPTOMS	Fever (in the absence of neutropenia, where neutropenia is defined as		

Agent Specific Adverse Events Agent Name: OXALIPLATIN			
	AGC<1.0 x 10e9/L)		
CONSTITUTIONAL SYMPTOMS	Weight loss		
DERMATOLOGY/SKIN	Alopecia		
DERMATOLOGY/SKIN	Hand-foot skin reaction		
DERMATOLOGY/SKIN	Injection site reaction		
DERMATOLOGY/SKIN	Rash/desquamation		
ENDOCRINE	Hot flashes/fluxes		
GASTROINTESTINAL	Anorexia		
GASTROINTESTINAL	Constipation		
GASTROINTESTINAL	Dehydration		
GASTROINTESTINAL	Diarrhea patients with colostomy		
GASTROINTESTINAL	Diarrhea patients without colostomy		
GASTROINTESTINAL	Dysphagia, esophagitis, odynophagia (painful swallowing)		
GASTROINTESTINAL	Gastrointestinal-Other (Specify,____)	Gastrointestinal reflux	
GASTROINTESTINAL	Gastrointestinal-Other (Specify,____)	Enteritis	Specify site of enteritis
GASTROINTESTINAL	Gastrointestinal-Other (Specify,____)	Ascites (NOS)	
GASTROINTESTINAL	Gastrointestinal-Other (Specify,____)	Intestinal obstruction	
GASTROINTESTINAL	Ileus (or neuroconstipation)		
GASTROINTESTINAL	Nausea		
GASTROINTESTINAL	Stomatitis/pharyngitis (oral/pharyngeal mucositis)		
GASTROINTESTINAL	Taste disturbance (dysgeusia)		
GASTROINTESTINAL	Vomiting		
HEMORRHAGE	CNS hemorrhage/bleeding		
HEMORRHAGE	Hemoptysis		
HEMORRHAGE	Hemorrhage-Other (Specify,____)	Hemorrhage NOS	
HEMORRHAGE	Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia		
HEMORRHAGE	Melena/GI bleeding		
HEMORRHAGE	Rectal bleeding/hematochezia		
HEPATIC	Alkaline phosphatase		
HEPATIC	Bilirubin		
HEPATIC	GGT (Gamma-Glutamyl transpeptidase)		
HEPATIC	Hepatic enlargement		
HEPATIC	SGOT (AST) (serum glutamic oxaloacetic transaminase)		
HEPATIC	SGPT (ALT) (serum glutamic pyruvic transaminase)		
INFECTION/ FEBRILE NEUTROPENIA	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10e9/L, fever >=38.5 degrees C)		
INFECTION/ FEBRILE NEUTROPENIA	Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10e9/L)		
INFECTION/ FEBRILE NEUTROPENIA	Infection with unknown ANC		
INFECTION/ FEBRILE NEUTROPENIA	Infection without neutropenia		

Agent Specific Adverse Events Agent Name: OXALIPLATIN			
METABOLIC/LABORATORY	Acidosis (metabolic or respiratory)		
METABOLIC/LABORATORY	Hyperuricemia		
METABOLIC/LABORATORY	Hypocalcemia		
METABOLIC/LABORATORY	Hypokalemia		
METABOLIC/LABORATORY	Hypomagnesemia		
METABOLIC/LABORATORY	Hyponatremia		
METABOLIC/LABORATORY	Hypophosphatemia		
MUSCULOSKELETAL	Musculoskeletal-Other (Specify,____)	Involuntary muscle contractions	
NEUROLOGY	Ataxia (incoordination)	Including abnormal gait	
NEUROLOGY	Insomnia		
NEUROLOGY	Mood alteration-depression		
NEUROLOGY	Neuropathy - cranial	Ptosis	
NEUROLOGY	Neurology - sensory		Including acute laryngopharyngeal dysesthesias, hyporeflexia, Lhermitte's sign, Paresthesia
NEUROLOGY	Vertigo		
OCULAR/VISUAL	Conjunctivitis		
OCULAR/VISUAL	Ocular/Visual-Other (Specify, ____)	Vision abnormal	Includes blindness, optic neuritis, papilledema, Hemianopsia, visual field defect
PAIN	Abdominal pain or cramping		
PAIN	Arthralgia (joint pain)		
PAIN	Bone pain		
PAIN	Chest pain (non-cardiac and non-pleuritic)		
PAIN	Headache		Including migraine
PAIN	Myalgia (muscle pain)		Including cramps and leg cramps
PULMONARY	Cough		
PULMONARY	Dyspnea (shortness of breath)		
PULMONARY	Hiccoughs (hiccups, singultus)		
PULMONARY	Pneumonitis/pulmonary infiltrates		Including eosinophillic pneumonia, interstitial pneumonitis, interstitial lung diseases
PULMONARY	Pulmonary fibrosis		
PULMONARY	Pulmonary-Other (Specify, ____)		Laryngo spasm
RENAL/GENITOURINARY	Creatinine		Increased
RENAL/GENITOURINARY	Renal failure		
RENAL/GENITOURINARY	Urinary retention		

The CRFs for subjects who had discontinued Protocol therapy for toxicity, side effects, or complications were reviewed initially for the accuracy of the data in the Retrospective Bevacizumab Dose Modification Form (completed for approximately 85% of subjects on the bevacizumab monotherapy and FOLFOX4 + bevacizumab arms). During this selected spot check of CRF data the following concerns were noted:

- Corrections to the CRFs were made as long as 2 ½ years after the initial CRF was submitted to ECOG. There is no documentation if the change was due to an inquiry, or the reasons for the change.
- There is no documentation of the dates or cycle days that any component of FOLFOX4 chemotherapy was administered if the retrospective "Bevacizumab Dose Modification Form" was not completed.
- The prospective CRFs document only the date of initiation and cessation of chemotherapy, and the total number of cycles administered.
- Multiple instances of chemotherapy being held were encountered without notation as to the toxicity or other reasons for the delay in administration of the chemotherapy.
- Laboratory and vital sign data used for the determination of protocol required dose reductions or discontinuation of bevacizumab can not be verified as this data was not collected.
- Toxicity CRFs were missing.

The following descriptions are just a few examples of the concerning CRFs noted.

- Subject 34005 had no toxicity form submitted.
- Subject 32463 had first protocol therapy given 1/27/03. Bevacizumab treatment was discontinued without a preceding dose reduction on 2/24/03. Protocol therapy was last administered on 4/29/03. Grade 2 proteinuria was noted on the Bevacizumab Dose Modification form. The Toxicity Form was corrected 2 years after the subject died. Grade 4 Atrial Fibrillation was coded on the Toxicity Form during the 04/14/03 to 05/17/03 adverse event reporting period received by ECOG on Dec 2, 2003 and was crossed out on 06/15/05 and received by ECOG on 06/24/05. The narrative provided for this subject describes the grade 4 atrial fibrillation event that appears to have led to heart failure and death.
- Subject 33073 has no toxicities listed on the Toxicity Form. The Treatment Summary Form documents that first protocol therapy was given on 08/20/02 and the last treatment on 01/22/03, with a total number10 cycles administered. The Treatment Summary Form states the "patient was taken off of study for platelets and ANC too low times 2 weeks". The retrospective Bevacizumab Dose Modification Form documents bevacizumab and FOLFOX4 chemotherapy being held on 6 occasions (10/01/02, 10/15/02, 11/05/02, 11/12/02, 01/02/03, 02/04/03) without notation in any of the CRFs as to the reasons for the doses being held.
- Subject 32323 initially had Grade 3 Syncope and Grade 3 hematemesis recorded from reporting period 12/09/02 to 1/28/03 on the Toxicity Form signed on 3/19/03 that was received by ECOG on 3/27/03. This report was changed to "Hemorrhage other" and the Grade 3 syncope event was removed on 6/25/05 and the form received by ECOG on 6/30/05.
- Subject 32582 received one course of FOLFOX4 + bevacizumab chemotherapy. The bevacizumab dose modification form notes Grade 2 fatigue and Grade 2 diarrhea with

colostomy (revised 4/13/05). The Toxicity Form received by ECOG on Sep 25 2003 initially had Grade 1 anorexia, Grade 2 diarrhea without colostomy and Grade 2 fatigue. The diarrhea and anorexia toxicities were crossed out with a notation of TH/ECC 10/19/03 and the fatigue was changed to Grade 3 without notation or date.

In summary, the data from the incompletely collected Retrospective Bevacizumab Dose Modification Form cannot be adequately assessed for accuracy by review of the data prospectively collected in the Toxicity CRF, Treatment Summary Form and laboratory data CRF (for which none exists). The safety data from a study conducted such that the specific toxicities warranting dose modifications or discontinuation of investigational agent, yet the respective toxicities, vital signs, and laboratory data responsible for the modifications to investigational agent administration are not captured, illustrates the suboptimal clinical study design of the E3200 trial.

In addition, numerous inconsistencies between the clinical study report (CSR) and the CRF data have been identified during the review of the Bevacizumab Dose Modification data. For example:

A review of Listing 16.2/7, page 2916 of the CSR reveals subject 32119 had bevacizumab dose reduced after experiencing Grade 3 hallucinations. The CRF documents hallucinations on 3/11/03 and a crossed out adverse event of ANC of 1456 on 3/25/02 one day prior to the planned 2nd cycle of chemotherapy. The CRFs for this subject show that the chemotherapy was held after the first cycle and the Grade 3 hallucinations, and then subsequently dose reduced on 4/17/02 for Grade 2 vaginal bleeding documented in the Retrospective Bevacizumab Dose Modification Form on 4/01/02.

The Summary CRF documents the following comment:

mments Bevacizumab dose was ↓ to 5mg/kg due to G2 vaginal bleeding following cycle 1 treatment

The Summary CRF states that the reason treatment ended was for: Toxicity/side effects/complications. However, no further notation or documentation of either a new toxicity or ongoing toxicity for the discontinuation of treatment is provided in the CRFs. The only adverse event documented in the Toxicity CRF is Grade 3 hallucinations. The grade 2 vaginal bleed was not required to be recorded in the Toxicity CRF.

Subject 32261 (FOFLX4 + bevacizumab) as documented in the CSR line listing 16.2/7 showed bevacizumab was dose reduced for Grade 2 Fatigue. Review of the CRF shows that a dose reduction occurred for Grade 2 proteinuria with an onset date of 11/13/2002:

R E 0 8 Proteinuria 2 11/13/2002 06 3

However, the first dose reduction of bevacizumab (Retrospective Bevacizumab Dose Modification Form) is documented on 02/03/03.

Bevacizumab Dose History

Prescribed Agent Dose 1=10mg/kg 2=5mg/kg	Bevacizumab Dose Administered (mg)	Date Bevacizumab Given M D Y	Source for treatment administration data reported on this form: 1=Nurse chemotherapy treatment record 2=Physician order 3=Clinic notes 4=DARF 5=Other - specify in applicable row(s) below
1	810 mg	08/21/2002	2, 1
1	773 mg	09/04/2002	2, 1
1	784 mg	09/18/2002	2, 1
1	784 mg	10/02/2002	2, 1
1	768 mg	10/30/2002	2, 1
2	374 mg	02/03/2003	2, 1
	mg	/ /	

There is discrepancy between the dose history (an apparent 3 month holding of chemotherapy between 10/30/02 and 02/03/03) and the Treatment Summary CRF that documents the first date of protocol therapy was given on 8/21/02 and the last date of protocol therapy was given on 02/04/03 with 11 total cycles administered.

First date protocol therapy was given: 08/21/02 (M/D/Y)

Last date protocol therapy was given: 02/04/03 (M/D/Y)

Reason treatment ended

Choose one:

1 ☐ Treatment completed per protocol criteria
2 ☐ Disease progression, relapse during active treatment
3 ☒ Toxicity/side effects/complications
4 ☐ Death on study
5 ☐ Patient withdrawal or refusal after beginning protocol therapy
6 ☐ Alternative therapy (complete the ECOG Non-Protocol Therapy Form)
7 ☐ Other complicating disease Specify complicating disease_____
99 ☐ Other Specify other reason_____

Treatment Schedule - Systemic Therapy

Total number of cycles given: 11 (1 cycle = 2 weeks)

Were there any dose modifications or additions/omissions to protocol treatment?

Choose one:

1 ☐ No
2 ☑ Yes

ENTERED
Mar 24 03

If yes, choose one:

1 ☑ Planned (i.e., the treatment was changed according to protocol guidelines)
2 ☐ Unplanned (i.e., the treatment change was not part of protocol guidelines)
Name of therapy_____
Type of therapy modification_____
Reason for therapy modification_____
ECOGCC MAR 24 2003
3 ☐ Both planned and unplanned, specify unplanned changes above

-1 ☐ Unknown

It is not possible to determine the dose reduction of bevacizumab in relation to adverse events, the dosing of bevacizumab in relation to continuing adverse events, or the discontinuation of bevacizumab in relation to adverse events.

7.1.1 Deaths

FDA attempted to compare the frequencies of various adverse events within 4 weeks of death between the FOLFOX4 + bevacizumab arm and FOLFOX4 arm in order to determine if events other than progressive disease may have been involved in the cause of death. The manner of collection of safety data, most notably the lack of adverse event onset dates and 3 month "reporting periods", in Study E3200 did not allow for this analysis.

The Applicant states the adverse event data set provided for review was compiled from 7 sources. As noted previously the AdEERS data was reported differently by treatment arm and therefore is not useful for comparative purposes. The safety data base also used retrospectively

compiled toxicities gathered during the completion of the Bevacizumab Dose Modification Form (completed in only 85% of subjects who received bevacizumab or FOLFOX4 + bevacizumab). Reporting requirements per protocol stated that adverse events were to be recorded in the E3200 Toxicity Form for EPP and non-EPP patients. There were 41 subjects enrolled under the Expanded Participation Program, implemented to increase patient and physician access to NCI-sponsored trials. When only the data from the E3200 Toxicity Forms are used for analysis, eight Grade 5 adverse events are identified. The sponsor provides 21 CRFs for subjects who died of a cause other than progressive disease occurring up to 30 days after the last dose of protocol therapy. See Table 14: Grade 5 Adverse Events for an analysis of total Grade 5 adverse events as recorded in the Adverse Event data set by acquisition mechanism.

The Applicant provided 19 narratives for subjects on the FOLFOX4 + bevacizumab or bevacizumab monotherapy arms who died of a cause other than progressive disease occurring up to 30 days after the last dose of protocol therapy. The Applicant did not provide any corresponding narratives for subjects on the FOLFOX4 arm for deaths, toxicities, or selected adverse events. The Applicant did provide 4 CRFs for subjects who died of a cause other than progressive disease occurring up to 30 days after the last dose of protocol therapy. No subjects in the FOLFOX4 arm were observed to have died because of previously described bevacizumab related toxicities, whereas three GI perforations, 2 CNS hemorrhages, one GI bleed and one perioperative demise were noted as the cause of death in subjects who received bevacizumab. In addition 4 cases of death secondary to infections were noted in the FOLFOX4 +bevacizumab arm compared to only one in the FOLFOX4 arm. Genentech's assessment of these Grade 5 adverse events, as reflected in Table 34 of the CSR reproduced here as Table 13: Death within 30 days of Protocol Therapy, does not agree with this reviewer's assessment.

Table 13: Death within 30 days of Protocol Therapy

Cause of Death for Deaths within 30 Days of the Last Dose of Protocol Therapy: Treated Patients

	FOLFOX4 (n=285)	FOLFOX4 + Bevacizumab (n=287)	Bevacizumab (n=234)
Total deaths	11 (3.9%)	18 (6.3%)	20 (8.5%)
Due to this disease	7 (2.5%)	8 (2.8%)	11 (4.7%)
Due to protocol therapy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Both disease and therapy [a]	0 (0.0%)	1 (0.3%)	0 (0.0%)
Due to other cause	3 (1.1%)	6 (2.1%)	3 (1.3%)
Unknown	0 (0.0%)	1 (0.3%)	3 (1.3%)
Not stated	1 (0.4%)	2 (0.7%)	3 (1.3%)

Reviewer assessment of narratives and CRFs for subjects who died of a cause other than progressive disease occurring up to 30 days after the last dose of protocol therapy.

Subjects on the bevacizumab monotherapy arm:

32009 (Progressive disease)
32100 (Rapid decompensation during the first week after beginning bevacizumab treatment, associated with nausea, vomiting and cramps, Grade 5 acute respiratory failure)
32125 (Grade 5 gastrointestinal perforation)
32184 (Grade 5 infection/pneumonia)
32354 (Grade 4 CNS ischemia and Grade 5 CNS hemorrhage)
32370 (Progressive disease)
33085 (Died of unknown cause seven days after surgery for bowel obstruction)
33090 (Unknown, narrative notes that the CRF provided discrepant dates of treatment)
33115 (Grade 5 bowel perforation)

Subjects on the FOLFOX4 + bevacizumab arm:

32084 (Candida albicans fungemia)
32244 (Grade 5 infection/pneumonia)
32463 (Infection/pneumonia with neutropenia followed by supraventricular arrhythmias and CHF)
32513 (Grade 5 constitutional symptoms/sudden death possible PE)
32541 (Grade 5 aspiration)
33033 (Grade 4 hypertension followed by Grade 5 CNS hemorrhage)
33060 (Grade 5 gastrointestinal bleed)
33117 (Probable progressive disease)
34037 (Neutropenia, Sepsis, ARDS)
34042 (Pelvic fracture followed by pneumonia)

Subjects on the FOLFOX4 arm:

33178 (Unknown, possible esophageal infection)
32197 (Pulmonary embolism)
32459 (Small bowel obstruction followed by aspiration pneumonia)
33006 (Food borne diarrhea followed by DIC picture and hepatorenal syndrome)

Table Table 14: Grade 5 Adverse Events depicts the number of Deaths within 30 days of the last administration of treatment and the adverse event reporting mechanism employed. "Constitutional symptoms" was used as a second term for progressive disease. Table 14 highlights that on the FOFLOX + bevacizumab arm there were 10 deaths not classified as "progressive disease" or "constitutional symptoms" that were not reported on the E3200 Toxicity Form as the events were considered by the investigator to be "unlikely", or "unrelated" to treatment.

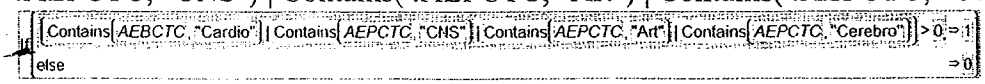
Table 14: Grade 5 Adverse Events

	FOLFOX4 (n=285)	FOLFOX4 + bevacizumab (n=287)	Bevacizumab (n=234)
Number of Subjects (Percent)			
Grade 5 Adverse event			
E3200 Toxicity Form	0 (0%)	3 (1%)	5 (2%)
Toxicity Form and AdEERS	11 (4%)	17 (6%)	17 (6%)
7 source compilation of AE data	11 (4%)	17 (6%)	17 (6%)
Grade 5 Adverse event (minus constitutional symptoms)			
E3200 Toxicity Form	0 (0%)	3 (1%)	5 (2%)
Toxicity Form and AdEERS	5 (2%)	13 (5%)	7 (3%)
7 source compilation of AE data	5 (2%)	13 (5%)	7 (3%)

7.1.2 Other Serious Adverse Events

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 coded as Thrombosis/embolism or (Cardiac troponin, Cardiac-ischemia, Cerebrovascular ischemia, Peripheral artery ischemia) and 38 subjects were identified. This approach identified all the subjects for whom the sponsor provided CRFs for adverse events designated arteriothromboembolic events. Twenty five subjects were coded as having incurred an adverse event listed in the AEPCTC column as Thrombosis/embolism and in the AESVTE column as "Venous thromboembolism". One of Seven subjects (Subject 33038) coded as having incurred a Grade 4 thrombosis/embolism event sub-classified as venous in nature contains no documentation in the CRF of a thrombosis/embolism adverse event.

Nineteen subjects were coded as having Grade 3 venous related thrombosis/embolism adverse events. The CRFs for subjects 34002 and 32045 contained no documentation of the venous nature of the adverse event. The CRF for subject 32526 stated the event was a femoral artery thrombus. Five subjects had no CRFs available for review.

Noting the serious limitations of the Adverse Event data sets and CRFs as described above, the FOLFOX + bevacizumab arm had 7 subjects who incurred 8 arteriothromboembolic events (one subject had an MI and a femoral artery thrombus). The bevacizumab monotherapy arm had 5 subjects and the FOLFOX4 arm had 2 subjects with arteriothromboembolic events. The increased incidence of arteriothromboembolic adverse events in subjects receiving bevacizumab is consistent with prior experience; however, this study suggests that bevacizumab monotherapy without concomitant chemotherapy also increases the incidence of arteriothromboembolic adverse events.

Gastrointestinal Perforation Related Adverse Events

The Applicant states the following in the CSR regarding adverse events related to GI perforation:

> *NCI AdEERS reporting requirements differed significantly between the treatment arms of the study. Therefore, since the estimate of the incidence of these events is based in part on NCI AdEERS data, comparisons of the incidence of these events between treatment arms should be interpreted with caution. Of note, the following NCI-CTC version 2.0 terms include gastrointestinal perforation in their definition: colitis, proctitis, typhlitis, duodenal ulcer, gastric ulcer, and dysphagia/esophagitis/odynophagia. Some of these events (colitis, typhlitis, and dysphagia/esophagitis/odynophagia) did not require expedited reporting in NCI AdEERS for the FOLFOX4 arm. Therefore, it is possible that gastrointestinal perforation events in the FOLFOX4 arm associated with these terms were not reported in NCI AdEERS.*

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 E3200 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 E3200.
2. Verbatim adverse event terms were not collected on the E3200 Toxicity Form.
3. Fistula events not considered related to protocol therapy were not collected on the E3200 Toxicity Form.

The Applicant performed a review of AdEERS and E3200 Toxicity form data in order to identify possible perforation related events. The Applicant review was conducted as follows:

1. E3200 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.

Table 15: All Potential Gastrointestinal Perforation Related Adverse Events depicts all potential gastrointestinal perforation related adverse events regardless of the attribution to GI perforation as determined by the investigator. The incidence of adverse events related to GI perforation is similar to the rates observed in the previously conducted studies AVF2192g and AVF2107g.

Table 15: All Potential Gastrointestinal Perforation Related Adverse Events

	FOLFOX4 (n=285)	FOLFOX4 + bevacizumab (n=287)	Bevacizumab (n=234)
Number of Subjects (Percent)			
Total GI perforation related AEs	1 (0.4%)	9 (3.1%)	7 (3.0%)
GI Perforation	0 (0%)	5 (1.7%)	4 (1.7%)
Intra-abdominal abscess	0 (0%)	6 (2.1%)	2 (0.9%)
Fistula	1 (0.4%)	5 (1.7%)	3 (1.3%)

7.1.3 Dropouts and Other Significant Adverse Events

The proportion of patients who discontinued all protocol therapy for toxicity was similar between the FOFLOX4 (24%) and FOLOFX4 + bevacizumab (23%) treatment arms. The E3200 study did not identify the toxicities responsible for discontinuation of protocol therapy due to toxicity, therefore accurate description of dropouts secondary to toxicity is not possible. The retrospective bevacizumab discontinuation form documents that 70 patients of 241 with completed forms (29%) discontinued bevacizumab treatment. The Applicant notes that 37 of the 70 patients had adverse events listed that did not include adverse events specified in the protocol as requiring bevacizumab discontinuation. At least 12% of subjects who discontinued bevacizumab continued to receive at least one or more cycles of some component of FOLFOX4 chemotherapy.

7.1.5 Common Adverse Events

Adverse event data from Study E3200 should be used with caution for quantitative comparisons of events between treatment arms because of the previously described confounding factors in adverse event collection and ascertainment bias in the retrospective nature of the adverse event data collection on the bevacizumab dose modification forms.

Twenty-seven diarrhea adverse events were reported via AdEERS, 9 of 27 subjects did not have a corresponding diarrhea adverse event recorded on the E3200 Toxicity CRF. Eight of 9 diarrhea adverse events not recorded were Grade 1 or 2 and were not required to be captured on the E3200 Toxicity Form. See Table 16: Correlation of Diarrhea Adverse Events reported via AdEERS and the E3200 Toxicity Form.

The Adverse Event data set provided by the Applicant was compiled from the following 7 sources:

AESRC Text String	Adverse Event Collection Mechanism
AdEERS	NCI AdEERS
Dose Discontinuation Form 2112	Discontinuation section of the E3200 Bevacizumab Dose Modification Form
Dose Reduction Form 2112	Dose Reduction section of the E3200 Bevacizumab Dose Modification Form
On-Study (EPP)	E3200 On-Study Form for EPP
On-Study Form 1559 (non-EPP)	E3200 On-Study Form for non-EPP
Toxicity (EPP)	Toxicity Form for EPP
Toxicity Form 1560 (non-EPP)	E3200 Toxicity Form for non-EPP

AdEERS=Adverse Event Expedited Reporting System; EPP=Expanded Participation Project; NCI=National Cancer Institute.

Table 16: Correlation of Diarrhea Adverse Events reported via AdEERS and the E3200 Toxicity Form

Subject number	AdEERS	AdEERS Adverse Event Onset Date	3200 Toxicity Form	Toxicity Form Reporting Period	AdEERS Attribution to protocol therapy
32033	X (Grade 1 and 2)	05/28/02			Possible
32042	X (Grade 2)	01/24/02			Definite
32131	X (Grade 1)	08/26/02			Probable
32205	X (Grade 2)	08/13/02			Probable
32251	X	08/27/02	X	(08/13/02-10/04/02)	
32265	X	08/20/02	X	(08/20/02-09/17/02)	
32274	X	01/27/02	X	(01/27/02-02/10/03)	
32290	X	09/03/02	X	(08/28/02-09/27/02)	
32293	X	01/12/03	X	(01/06/03-01/28/03)	
32294	[redacted]	12/04/02	X	(Dates do not overlap)	Definite
32381	X (Grade 2)	12/02/02			Possible
32462	X (Grade 2)	01/21/03			Possible
32466	X	03/27/03	X	(03/20/03-04/23/03)	
32474	X	02/20/03	X	(01/30/02-03/06/03)	
32483	X	02/16/03	X	(02/11/03-03/11/03)	
32514	X	04/29/03	X	04/02/03-05/19/03)	
32554	X (Grade 1)	11/28/03			Possible
32572	X (Grade 2)	04/26/03			Definite
32583	X	05/18/03	X	(xx/xx/xx-05/27/03)	
33006	X	03/13/02	X	(01/21/02-03/23/02)	
33034	X	04/13/02	X	(03/13/02-06/23/02)	
33034	X	06/10/02	X	(03/13/02-06/23/02)	
33046	X	11/29/02	X	(11/02/02-12/20/02)	
33118	X	12/28/02	X	(11/26/02-12/30/02).	
33128	X (Grade 1)	06/14/03			Probable
33164	X	04/19/03	X	(03/25/03-04/21/03)	
33179	X	04/10/03	X	(04/02/03-05/02/03)	
34002	X	05/08/02	X	(04/24/02-05/14/02)	
34002	X	10/28/03	X	(10/14/03-11/11/03)	

The FDA analyzed the Adverse Event data set provided for review and produced Table 17: Grade 3 and 4 Adverse Events which shows the number of subjects that had one or more selected Grade 3 or 4 adverse events based on the data contained in the E3200 Toxicity Form, Toxicity Form and AdEERS reporting, and the complete 7 source compilation of adverse event data. This analysis was essentially in agreement with Genentech's analysis (see Table 18: E3200 Toxicity Form Reported Adverse Events reproduced from Table 28, page 101 of the CSR). However, when the 7-source compilation data set is used for analysis, there were 8 additional cases of hypertension noted in the FOLFOX + bevacizumab arm. The adverse event data recorded in the

E3200 Toxicity Form was filtered at the level of the investigator based on attribution to investigational agent of "possibly", "probably", or "definite".

Table 17: Grade 3 and 4 Adverse Events

	FOLFOX4 (n=285)	FOLFOX4 + bevacizumab (n=287)	Bevacizumab (n=234)
Number of Subjects (Percent)			
Diarrhea			
E3200 Toxicity Form	36 (13%)	51 (17%)	5 (2%)
Toxicity Form and AdEERS	36 (13%)	51 (17%)	5 (2%)
7 source compilation of AE data	36 (13%)	51 (17%)	5 (2%)
Nausea			
E3200 Toxicity Form	12 (4%)	31 (11%)	8 (3%)
Toxicity Form and AdEERS	13 (5%)	35 (12%)	13 (5%)
7 source compilation of AE data	13 (5%)	35 (12%)	14 (6%)
Vomiting			
E3200 Toxicity Form	9 (3%)	29 (10%)	11 (5%)
Toxicity Form and AdEERS	10 (3%)	32 (11%)	15 (6%)
7 source compilation of AE data	11 (4%)	32 (11%)	15 (6%)
Neuropathy-sensory			
E3200 Toxicity Form	26 (9%)	48 (17%)	2 (1%)
Toxicity Form and AdEERS	27 (9%)	49 (17%)	3 (1%)
7 source compilation of AE data	27 (9%)	50 (17%)	3 (1%)
Headache			
E3200 Toxicity Form	1 (0.4%)	8 (3%)	2 (1%)
Toxicity Form and AdEERS	1 (0.4%)	9 (3%)	5 (2%)
7 source compilation of AE data	1 (0.4%)	9 (3%)	5 (2%)
Hypertension			
E3200 Toxicity Form	5 (2%)	18 (6%)	17 (7%)
Toxicity Form and AdEERS	5 (2%)	19 (7%)	17 (7%)
7 source compilation of AE data	7 (2%)	26 (9%)	19 (8%)
Hemorrhage			
E3200 Toxicity Form	1 (0.4%)	11 (4%)	7 (3%)
Toxicity Form and AdEERS	2 (0.7%)	14 (5%)	9 (4%)
7 source compilation of AE data	2 (0.7%)	15 (5%)	9 (4%)
***Hemorrhage other**			
E3200 Toxicity Form	0 (0%)	6 (2%)	1 (0.4%)
Toxicity Form and AdEERS	0 (0%)	6 (2%)	1 (0.4%)
7 source compilation of AE data	0 (0%)	7 (2%)	1 (0.4%)

Hemorrhage = CNS hemorrhage, hemetemesis, hematuria, hemorrhage associated with surgery, hemorrhage with grade 3 or 4 platelets, hemorrhage without grade 3 or 4 platelets, hemorrhage-other, melena/GI bleeding, rectal bleeding.

Table 18: E3200 Toxicity Form Reported Adverse Events

Table 28

Grade 3–5 Non-Hematologic and Grade 4 and 5 Hematologic Toxicities Considered to Be Related to Protocol Therapy (≥2% Increase in Incidence): Treated Patients

NCI-CTC Terminology	FOLFOX4 (n=285)	FOLFOX4 + Bevacizumab (n=287)	Bevacizumab (n=234)
Patients with at least one event	171 (60.0%)	219 (76.3%)	87 (37.2%)
Gastrointestinal			
Diarrhea	36 (12.6%)	51 (17.8%)	4 (1.7%)
Nausea	12 (4.2%)	31 (10.8%)	7 (3.0%)
Vomiting	9 (3.2%)	29 (10.1%)	10 (4.3%)
Dehydration	14 (4.9%)	25 (8.7%)	8 (3.4%)
Ileus	1 (0.4%)	8 (2.8%)	5 (2.1%)
Neurology			
Neuropathy–sensory	26 (9.1%)	47 (16.4%)	2 (0.9%)
Neurologic–other	8 (2.8%)	15 (5.2%)	3 (1.3%)
Constitutional symptoms			
Fatigue	37 (13.0%)	53 (18.5%)	10 (4.3%)
Pain			
Abdominal pain	10 (3.5%)	17 (5.9%)	12 (5.1%)
Headache	0 (0.0%)	8 (2.8%)	3 (1.3%)
Cardiovascular (general)			
Hypertension	5 (1.8%)	18 (6.3%)	17 (7.3%)
Pulmonary			
Dyspnea	11 (3.9%)	17 (5.9%)	3 (1.3%)
Hemorrhage			
Hemorrhage–other	0 (0.0%)	6 (2.1%)	1 (0.4%)

FOLFOX4=oxaliplatin/5-fluorouracil/leucovorin.

Note: NCI-CTC version 2.0. This table includes events as reported on the E3200 Toxicity Form with a ≥2% increase in incidence in either bevacizumab-containing arm compared with the FOLFOX4 arm. In addition, 7 patients (3.0%) in the bevacizumab monotherapy arm reported a Grade 3–5 bilirubin event (Grade 5, 0.4%).

Common Adverse Events of Particular Interest

Neuropathy

An accurate assessment of the incidence of neuropathy adverse events was not possible as adverse events in Study E3200 were reported as the worst grade of an event for a patient during a reporting period, which was 1 month in duration during the first six cycles of treatment and 3 months in duration thereafter. Neither the specific onset date of an adverse event nor the exact cycle in which an adverse event occurred was captured. Thus, the incidence of Grade ≥ 3 neurotoxic events appears to increase for the FOFLOX4 + bevacizumab treatment arm since fewer subjects are at risk for reporting neuropathy in the FOLFOX4 arm compared with the FOLFOX4+bevacizumab arm in the later reporting periods. Table 19: Neuropathy Adverse Events by Reporting Period (reproduced from Genentech's 28-FEB-06 submission, Appendix D Table 3) summarizes the incidence of Grade 3–4 sensory neuropathy events only for treated subjects who remained at risk at the beginning of each reporting period. Subjects considered to be at risk were defined as those on protocol therapy at the beginning of a reporting period who had not experienced a prior Grade 3–4 sensory neuropathy event. The incidence of Grade 3–4 sensory neuropathy events was similar for the FOLFOX4-containing arms through the first 168 days (~6 months) of protocol therapy. In the 169 to 252-day reporting period, the higher incidence of neuropathy observed in the FOLFOX4 + bevacizumab arm may have been influenced by the between-arm difference in the number of subjects at risk during the entire 3 months of the reporting period, as opposed to those at risk at the beginning of that period. The incidence rates of neuropathy based on cumulative exposure of oxaliplatin are commensurate

with the literature data, however, a bevacizumab oxaliplatin synergistic toxicity/interaction cannot be ruled out based on the limitations of the adverse event collection data in study E3200.

Table 19: Neuropathy Adverse Events by Reporting Period

	FOLFOX4 (n=285)		FOLFOX4+ Bevacizumab (n=287)		Bevacizumab (n=234)	
Reporting Period	Patients at Risk at the Beginning of Time Period n (%) (a)	Grade 3-5 Sensory Neuropathy n (%) (b)	Patients at Risk at the Beginning of Time Period n (%) (a)	Grade 3-5 Sensory Neuropathy n (%) (b)	Patients at Risk at the Beginning of Time Period n (%) (a)	Grade 3-5 Sensory Neuropathy n (%) (b)
1 - 28 days	285 (100.0%)	4 (1.4%)	287 (100.0%)	6 (2.1%)	234 (100.0%)	0 (0.0%)
29 - 56 days	255 (89.5%)	1 (0.4%)	256 (89.2%)	1 (0.4%)	201 (85.9%)	0 (0.0%)
57 - 84 days	196 (68.8%)	1 (0.5%)	224 (78.0%)	2 (0.9%)	121 (51.7%)	1 (0.8%)
85 - 168 days	167 (58.6%)	13 (7.8%)	204 (71.1%)	18 (8.8%)	96 (41.0%)	0 (0.0%)
169 - 252 days	61 (21.4%)	6 (9.8%)	115 (40.1%)	20 (17.4%)	33 (14.1%)	0 (0.0%)
>= 253 days	18 (6.3%)	0 (0.0%)	49 (17.1%)	0 (0.0%)	15 (6.4%)	0 (0.0%)

7.1.5.1 Eliciting adverse events data in the development program

Neither ECOG nor the other cooperative groups involved in Study E3200 provided 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.

In addition, the study did not capture vital sign data; therefore, correlation of blood pressure measurements with the onset and duration of hypertensive adverse events cannot be performed. The study also did not capture basic laboratory data such as electrolytes, urinalysis results 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, NCI-CTC Adverse event Category and Organ System description. The CTC v2.0 Adverse Event dictionary contains approximately 400 terms. Sixteen percent of the data (reported through AdEERS) has a single MedDRA low level preferred term mapped to the CTC adverse event term. Further description of the adverse event categorization scheme is not provided in the CSR. This reviewer finds the granularity of the adverse event reporting in the CRTs provided for review inadequate for determining the nature of various adverse events such as angina and transient ischemic attacks.

7.1.5.4 Common adverse event tables

Table 20 was supplied by the Applicant. Incidence rates were checked for correlation with the CRT data. The data may be inaccurate based on the previous discussions of the deficiencies in the clinical study data. The adverse event data in the label was revised to include all adverse events collected from the "7 source compilation" adverse event data set provided by the Applicant (see table 17).

Table 20: Common Adverse Event Table as Presented by the Sponsor
Grade 3-5 Non-Hematologic and Grade 4 and 5 Hematologic Toxicities Considered Related to Protocol Therapy (≥2% Increase in Incidence)

NCI-CTC Terminology	FOLFOX4 (n=285)	FOLFOX4 + Bevacizumab (n=287)	Bevacizumab (n=234)
Patients with at least one event	171 (60.0%)	219 (76.3%)	87 (37.2%)
Gastrointestinal			
Diarrhea	36 (12.6%)	51 (17.8%)	4 (1.7%)
Nausea	12 (4.2%)	31 (10.8%)	7 (3.0%)
Vomiting	9 (3.2%)	29 (10.1%)	10 (4.3%)
Dehydration	14 (4.9%)	25 (8.7%)	8 (3.4%)
Ileus	1 (0.4%)	8 (2.8%)	5 (2.1%)
Neurology			
Neuropathy–sensory	26 (9.1%)	47 (16.4%)	2 (0.9%)
Neurologic–other	8 (2.8%)	15 (5.2%)	3 (1.3%)
Constitutional symptoms			
Fatigue	37 (13.0%)	53 (18.5%)	10 (4.3%)
Pain			
Abdominal pain	10 (3.5%)	17 (5.9%)	12 (5.1%)
Headache	0 (0.0%)	8 (2.8%)	3 (1.3%)
Cardiovascular (general)			
Hypertension	5 (1.8%)	18 (6.3%)	17 (7.3%)
Pulmonary			
Dyspnea	11 (3.9%)	17 (5.9%)	3 (1.3%)
Hemorrhage			
Hemorrhage–other	0 (0.0%)	6 (2.1%)	1 (0.4%)

7.1.7 Laboratory Findings

Laboratory data including complete blood counts and serum chemistries were not captured during the conduct of study E3200.

7.1.8 Vital Signs

Vital sign data was not captured during the conduct of study E3200 despite the fact that hypertension is a known complication of treatment with bevacizumab and that the study employed dose reduction and discontinuation criteria for hypertension.

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 E3200.

7.1.10 Immunogenicity

Immunogenicity studies were not performed during the conduct of study E3200.

7.1.11 Human Carcinogenicity

Human carcinogenicity studies were not conducted during study E3200. 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 E3200 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 are two-fold greater than 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 E3200 CSR.

7.1.17 Postmarketing Experience

The significant safety concerns of 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 285 subjects in the FOLFOX arm, 287 subjects in the FOLFOX + bevacizumab arm and 234 subjects in the bevacizumab monotherapy arm received at least one component of protocol therapy. The Applicant states that data were not available for exposure to individual components of protocol therapy. Accurate quantification of bevacizumab exposure is not

possible based on the data in the CRTs and CRFs. The median number of cycles of bevacizumab treatment in the FOLFOX4 + bevacizumab arm was 10.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

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

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience of this study was not adequate to make definitive statements regarding bevacizumab related toxicities secondary to the previously described limitations of the study design and conduct. All the materials provided for review were used to make the best possible assessment and generalization of the potential bevacizumab related toxicities.

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 based on investigator- and CTEP- determined attribution. This point is highlighted by numerous instances encountered during the review of CRFs, narratives, and CRTs where known toxicities associated with bevacizumab at that time or identified since than as bevacizumab associated toxicities were classified as unrelated or unlikely to be related by both the investigator and CTEP. In one instance, CTEP changed an investigator determined attribution of intestinal perforation from "possibly" related to "unlikely" to be related. The use of two toxicity recording mechanisms, (CTEP/AdEERS and E3200 Toxicity Forms) and differential reporting requirements by treatment arm also seriously limits the ability to assess adverse events. The fact that the Applicant 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. Although the study conduct is fraught with limitations, the data do not suggest any new bevacizumab related safety signals. 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 Prescribing Information: Intestinal perforation, hemorrhage, arteriothromboembolic events, hypertension, and proteinuria. Data from Study E3200 suggested an increased incidence of emesis in subjects who received FOLFOX + bevacizumab compared to subjects receiving FOLFOX alone that has not been previously seen with other chemotherapy regimens. The study data also revealed a possible relationship of bevacizumab increasing the incidence of Oxaliplatin induced peripheral neuropathy; unfortunately, the lack of recording of adverse event onset dates in study E3200 precludes our ability to adequately evaluate this interaction.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Comparisons of the results from Study E3200 with previous Genentech-sponsored studies using bevacizumab in CRC subjects was not considered useful or interpretable because of the

respective differences in prior therapy for metastatic disease (previously untreated vs. previously treated), the bevacizumab dose administered (5 mg/kg vs. 10 mg/kg), the chemotherapy regimen used (5-FU with or without irinotecan vs. 5-FU with oxaliplatin), and the method of collection of adverse events (all events regardless of their relationship to treatment vs. related events only).

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. Although this study utilized a single 10 mg/kg dose, subjects exhibiting grade 1 or 2 hypertension were dose reduced to 5 mg/kg. Based on the incomplete and retrospective bevacizumab toxicity assessment, the reduction in bevacizumab dose from 10 to 5 mg/kg resulted in the improvement or resolution of hypertension in 60-70% of subjects for which CRFs were collected (see Table 21: Dose Reduction Outcome for Hypertension and Proteinuria derived from table 39 of the CSR).The definition of "improved" is not described in the CSR, and as previously discussed, blood pressure measurements were not collected and therefore can not be reviewed to determine the accuracy of this information.

Although proteinuria also appears to have improved with a dose reduction of bevacizumab, the analysis of the data is confounded by the proteinuria dose modification rules whereby subjects did not have a repeat 24 hour urine protein collection after dose reduction. In addition, based on the dose reduction rules, a subject who had a second 24 hour protein determination performed (secondary to an increase in dip stick protein) would have bevacizumab discontinued for a protein level ≥500 mg/24 hours even if less than the initial 24 hour urine protein measurement that resulted in dose reduction (see Figure 5: Proteinuria Dose Modification Rules reproduced from Protocol E3200-A2 Section 5.3.3.2). This reviewer finds the proteinuria dose modification rules internally inconsistent, and questions the manner in which they were implemented. The dipstick- and 24 hour urine protein- measurements were not collected during the conduct of Study E3200.

Table 21: Dose Reduction Outcome for Hypertension and Proteinuria

NCI-CTC Terminology and Outcome	FOLFOX +bevacizumab (n=241)	Bevacizumab (n=202)
Hypertension	23 (9.5%)	9 (4.5%)
Resolved	10 (43.5%)	4 (44.4%)
Improved	8 (34.8%)	2 (22.2%)
No Change	5 (21.7%)	3 (33.3%)
Proteinuria	21 (8.7%)	14 (6.9%)
Resolved	12 (57.1%)	6 (42.9%)
Improved	3 (14.3%)	3 (21.4%)
No Change	6 (28.6%)	5 (35.7%)

Figure 5: Proteinuria Dose Modification Rules

5.332 Proteinuria

Any change in proteinuria from baseline (other than trace+) as determined by urine dipstick, requires holding bevacizumab treatment and performing a 24 hour urine collection to determine total protein. When bevacizumab is withheld to perform a 24-hour urine for total protein, that dose should be considered omitted. If the result of the 24-hour urine allows continued use of bevacizumab, the omitted dose should not be "made up" and the patient should receive the next scheduled dose.

If proteinuria is <500 mg/24 hours, continue bevacizumab without dose reduction.

If proteinuria is ≥500mg/24 hours, but ≤2 grams/24 hours, decrease all subsequent doses of bevacizumab to 5mg/kg.

If proteinuria is >2 grams/24 hours, bevacizumab may be held until it returns to ≤2 grams/24 hours and all subsequent doses reduced to 5mg/kg.

A 24 hour urine collection for total protein should be repeated only if there is a further increase in the urine dipstick findings from the value that resulted in the dose reduction as a repeat 24 hour urine for total protein.

If proteinuria is <0.5 grams/24 hours, continue bevacizumab at 5mg/kg.

If proteinuria is ≥0.5 grams/24 hours, decrease bevacizumab. (Patients on Arm A may continue to receive chemotherapy according to protocol. Patients on Arm C will discontinue protocol therapy.)

7.4.2.2 Explorations for drug-demographic interactions

Emesis and Ileus appear to be increased in subjects ≥ 65 years of age on the FOFLFOX + bevacizumab arm compared to the FOLFOX arm versus subjects less than 65 years of age as seen in Table 22: Adverse Events with an Increased Incidence in Subjects over 65 Years of Age. Caution should be used in interpreting these results as the number of events per arm in each specific category is small.

Table 22: Adverse Events with an Increased Incidence in Subjects over 65 Years of Age

Adverse events with an increased incidence in subjects ≥ 65 years of age

Toxicity fold increase {(65-74)/< 65}	NCI-CTC Grade	< 65 (n=355)		65-74 (n=147)		≥ 74 (n=69)	
		FOLFOX 4 (n=179)	FOLFOX4 /BV (n=176)	FOLFOX 4 (n=78)	FOLFOX4/ BV (n=69)	FOLFOX 4 (n=28)	FOLFOX4/ BV (n=41)
Nausea {2.2}	3	9 (5.0%)	18 (10.2%)	2 (2.6%)	8 (11.6%)	1 (3.6%	5 (12.2%)
Emesis {4.7}	3-4	6 (3.4%)	14 (8.0%)	1 (1.3%)	10 (14.5%)	2 (7.1%)	5 (12.2%)
Ileus {7.2}	3	1 (0.6%)	1 (0.6%)	0 (0.0%)	5 (7.2%)	0 (0.0%)	2 (4.9%)
Fatigue {1.4}	3-4	20 (11.2%)	25 (14.2%)	12 (15.4%)	19 (27.5%)	5 (17.9%)	9 (22.0%)

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosage of bevacizumab evaluated in Study E3200 was 10 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 mg/kg given once every 14 days as an IV infusion. The 10 mg/kg every 2 week dosing had to be decreased to 5 mg/kg every 2 weeks in 20% of the subjects on the FOLFOX + bevacizumab arm and 15% of the subjects on the bevacizumab monotherapy arm.

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 analysis based on race, gender and age was conducted for Study E-3200 and the results are presented in section 6.1.4.3 and 7.4.2.3. No data from Study E3200 suggested that dosing should be modified based on demographic characteristics.

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 ongoing as part of the post-marketing commitment for Avastin. Patient accrual has been reached and the final study report is planned to be submitted by the 31 December 2006 FDA milestone.

A waiver for the requirement of additional pediatric studies will be granted in association with this supplement, given that CRC 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 under each part of the sBLA. The FDA conducted a search of the literature and reviewed the submitted references.

8.7 Postmarketing Risk Management Plan

No issues were identified during review of this supplement that would require a postmarketing risk management plan.

9 OVERALL ASSESSMENT

9.1 Conclusions

The addition of bevacizumab to FOLFOX4 chemotherapy provided a statistically significant and clinically meaningful improvement in overall survival compared to FOLFOX4 alone in patients whose disease had progressed after adjuvant chemotherapy with 5-FU and irinotecan and in patients with advanced or metastatic disease who had received prior 5-FU and irinotecan. The secondary endpoints of PFS and ORR supported the improvement in overall survival. The safety profile of bevacizumab, as demonstrated in this study, did not reveal new significant safety signals or adversely impact on subject's quality of life. Subset analyses did not reveal any group that did not benefit from the addition of bevacizumab to FOLFOX4 chemotherapy. The bevacizumab monotherapy arm was discontinued because analyses of the efficacy data by the DMC suggested that the use of bevacizumab monotherapy was inferior to FOLFOX4. Due to early discontinuation of the bevacizumab monotherapy arm and the addition of chemotherapy to the treatment regimen of these subjects, no definitive statements can be made regarding the efficacy of bevacizumab monotherapy.

9.2 Recommendation on Regulatory Action

This reviewer recommends approval of the BLA efficacy supplement STN 125085.74 for the use of Avastin in combination with 5-fluorouracil-based chemotherapy as first- or second-line treatment of patients with relapsed, advanced, or metastatic carcinoma of the colon or rectum with modifications to the proposed labeling.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no requirements for specific risk management activities.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments.

9.4 Labeling Review

Multiple labeling meetings were held with the Applicant to negotiate acceptable Package Insert language. The label was modified by both the Applicant and FDA to increase readability primarily in the Warning and Adverse Event sections.

The Dosage and Administration section was revised to more definitively reflect the dose administered in the studies for which data have been provided to FDA for review of safety and efficacy. Please see section 10.2 for the agreed upon complete Package Insert language.

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

BLACK BOX-WARNING

- Separation of Gastrointestinal Perforation and Wound Healing Complications into 2 distinct warnings.

CLINICAL STUDIES

- Revised the section to include a description of Study E3200.
- Deleted the E3200 Efficacy Results Table and included the pertinent information from the table as text with a 95% confidence interval.
- Only included subgroup analyses that contained at least 100 patients on each treatment arm and that were thought to be clinically meaningful.
- Deleted the promotional language statements regarding treatment of patients with bevacizumab until disease progression.

INDICATIONS AND USAGE

- Revised the section to include treatment of patients in the second-line setting.

WARNINGS

- Separation of Gastrointestinal Perforation and Wound Healing Complications into 2 distinct warnings.
  - Revised the sections to increase readability yet maintain the meaning of the original warnings and the pertinent numerical data.
- Revised language to active tense when directing prescribers to discontinue or not initiate Avastin treatment in light of specific observations.
- The Hypertension Warning section was revised by moving the table regarding hypertension and aspects of the text to the Adverse Reactions section.
- Data from Study E3200 was incorporated into the determinations of incidence rates for specific events.
- Subsection on Proteinuria was revised for succinctness.
- Subsection on Congestive Heart Failure was revised for readability.

Pregnancy Category C

- Revised to more closely reflect the dosages used in the preclinical teratogenicity studies.

Geriatric Use

- Addition of data suggesting increased relative risk of certain adverse events in patients ≥ 65 years of age.

ADVERSE REACTIONS

- Section revised from Adverse Events to Adverse Reactions.
- Addition of updated exposure data.
- Addition of Study E3200 demographic data.
- Updated adverse event incidence rates based on Study E3200 adverse event data.
- Revised Venous Thromboembolic Events section to state the noted increased incidence of subsequent venous thromboembolic events first. The section was also revised to improve readability.
- Subsection on Immunogenicity was moved from the Precautions Section to the ADVERSE REACTIONS section.
- Table 6 was revised to reflect adverse events that occurred at a ≥ 5% difference between the IFL + Avastin and IFL + placebo treatment arms.
- Deleted the median duration of treatment exposure in the E3200 Study since the actual bevacizumab exposure history was not collected.
- Table 7 was revised to reflect adverse event incidences as derived from the "7 source compilation" adverse event data set.

Other Serious Adverse Events.

- Adverse Events that are expected in CRC patients were deleted.
- Adverse events already noted in the prior sections were deleted.

DOSAGE AND ADMINSTRATION

- The Dosage and Administration section was revised to more definitively reflect the dose administered in the studies for which data have been provided to FDA for review of safety and efficacy.

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 eight times as described below. In addition, the bevacizumab monotherapy arm was closed to further enrollment in March 2003 based on a review of early results by the ECOG DMC.

The **first amendment** was incorporated before the 30 October 2001 activation of the protocol.

The **second amendment** to the protocol was effective 16 October 2002. The entire document was revised. This amendment contained several substantive changes, as outlined below:

- Measurable disease was removed as a stratification factor.
- Guidelines regarding the simultaneous administration of oxaliplatin and leucovorin and instructions for the dilution of oxaliplatin in 250–500 mL of DSW were provided.
- The inclusion criterion regarding PTT changed from PTT within normal limits to PTT less than or equal to the institutional ULN.
- An inclusion criterion was added permitting patients who have relapsed within 6 months of concluding adjuvant therapy with 5-FU in combination with irinotecan to be eligible for the study.
- Patients with proteinuria that was considered due to the use of ureteral stents, and not due to nephropathy, were permitted to enter the study.
- The Adverse Event Reporting Requirements section was updated. Frequency of adverse event collection while on protocol therapy was changed from every 3 months to monthly for the first six cycles (approximately 12 weeks) and every 3 months thereafter.
- Clarified that patients on the FOLFOX4 + bevacizumab arm who required discontinuation of both 5-FU and oxaliplatin for toxicity could continue to receive bevacizumab.
- Clarified that patients in the FOLFOX4 arm who required discontinuation of both 5-FU and oxaliplatin for toxicity would be removed from the study.
- Clarified that patients in the FOLFOX4 + bevacizumab arm who required discontinuation of bevacizumab due to toxicity could continue to receive oxaliplatin and 5-FU.
- Clarified that patients in the bevacizumab monotherapy arm who required discontinuation of bevacizumab due to toxicity would be removed from the study.
- Clarified that patients who achieved a clinical CR may receive two additional cycles of treatment and then should be removed from the study.
- Clarified that patients who undergo surgical resection of all existing disease will be removed from the study and should have PR reported as best response to therapy.
- Information regarding the preparation and availability of bevacizumab was replaced with new language per NCI.
- The Suggested Patient Consent Form was updated.
- The EPP definition of expectedness was clarified.
- The Criteria for Expedited Adverse Event Reporting were updated.
- An NCI AdEERS Agent Specific Adverse Event list for bevacizumab and oxaliplatin was provided.

The **third amendment** to the protocol was effective 13 February 2003. The main changes for this amendment were as follows:

- The Adverse Event Reporting Requirements section was updated.
- The EPP Adverse Event Reporting was revised to be consistent with new adverse event requirements.

The **fourth amendment** to the protocol was effective J26 February2003. The substantive changes in this amendment were as follows:

- Clarified that bevacizumab should be discontinued if a repeat 24-hour urine collection was > 0.5 g/24 hr.
- The Statistical Considerations section was updated to account for expanded accrual. The planned enrollment was increased to 880 total patients.
- Clarified that hospitalizations for Grade 3 expected events do not require 24-hour notification.

The **fifth amendment** to the protocol was effective 28 May 2003. This amendment contained the following substantive changes:

- The regulatory submission guidelines for the Randomization Procedures was updated.
- Grade 1–4 infection without neutropenia was removed from the list of exclusions for expedited reporting for the FOLFOX4 + bevacizumab arm.
- Grade 1–4 constipation, ileus, or bowel obstruction, Grade 1–4 infection, with or without neutropenia or infection with unknown ANC, and Grade 1–4 SGOT/SPGT were removed from the list of exclusions for expedited adverse event reporting for the FOLFOX4 arm.
- Secondary AML/MDS reporting instructions were clarified.
- Dose modification guidelines for liver function test abnormalities were added.
- SGPT and alkaline phosphatase were added to the list of tests under Study Parameters, and the assessment schedule was changed from every 4 weeks while on treatment to prior to each treatment.
- Language regarding liver function test abnormalities was added to the side effects of bevacizumab.
- Bowel perforation and bowel dehiscence were added as possible side effects of bevacizumab.
- Reference to the Eloxatin. Package Insert for complete prescribing information was added.
- Guidelines for the collection and submission of biologic samples upon the development of AML/MDS were added to the body of the protocol and protocol Appendix II.
- The Suggested Patient Consent Form (protocol Appendix I) was updated.

The **sixth amendment** to the protocol was effective 19 December 2003. This amendment contained administrative changes as requested by the NCI. Changes in this amendment included the following:

- Reference to the availability of the larger vial size of bevacizumab was added.
- Rash and dyspnea were added as infusion or allergic reaction side effects of bevacizumab.
- Nausea, vomiting, colitis, stomatitis/pharyngitis, and intestinal obstruction were added as gastrointestinal side effects of bevacizumab.
- Cardiovascular, constitutional, skin, pulmonary, renal/genitourinary, and musculoskeletal side effects of bevacizumab were added.
- Hematologic side effects were revised to accommodate new information provided by the NCI regarding hemorrhage.

- Clarified that the relationship of pericardial effusion and decreased cardiac function with bevacizumab was unclear and that additional toxicities may be associated with combination chemotherapy.

The **seventh amendment** to the protocol was effective 26 January 2005. The substantive changes in this amendment were as follows:

- A paragraph regarding Study AVF2107g was added to the Introduction as recommended by NCI in its Bevacizumab Action Letter.
- Language for reporting other secondary malignancies was updated.
- Bevacizumab dose modification guidelines for arterial thromboembolic events were added as required by NCI in its Bevacizumab Action Letter.
- Information regarding hematologic side effects of bevacizumab was updated to include information as directed by NCI in its Bevacizumab Action Letter.
- The Informed Consent form was updated with new information regarding increased risk of thromboembolic events, using language provided by NCI in its Bevacizumab Action Letter.
- The updated Agent Specific Adverse Event List CTC version 2.0 for oxaliplatin was provided.

The **eighth amendment** to the protocol was effective 6 April 2005. Most of the changes were administrative. These changes included the following:

- References to the Agent Specific Adverse Event List with the Comprehensive Adverse Events & Potential Risks (CAEPR) List were deleted.
- Drug information for oxaliplatin, including other names, classification, mode of action and description, storage and stability, how supplied, preparation, route of administration, incompatibilities, availability, and nursing implications, was updated; Side Effects to Reported Adverse Events and Potential Risks were revised to match CAEPR; a contraindications section was added.
- The risks of oxaliplatin in the Patient Consent were updated to be consistent with CAEPR and the Drug Formulation and Drug Formulation and Procurement section.
- The Agent Specific Adverse Event List was changed to the CAEPR List for oxaliplatin.

Changes to Planned Analyses

The following analyses were specified in SAP but were not performed because of the strong efficacy results.

- Exploratory analyses of PFS and objective response by baseline risk factor subgroups
- Exploratory multivariate modeling of the effect of risk factors on PFS and objective response

The following analyses were performed differently from the method specified in the final SAP:

- The SAP specified that ancillary comparisons of the bevacizumab monotherapy arm versus the other two treatment arms would be performed using only those patients from the two principal arms (FOLFOX4 + bevacizumab, FOLFOX4) who were enrolled prior to cessation of enrollment in the bevacizumab monotherapy arm. However, a comparison against the full population would provide a more inclusive analysis. Therefore, all comparisons with the bevacizumab monotherapy arm included all patients enrolled in the other two treatment arms. Additionally, providing these summaries using only concurrently enrolled patients would be largely redundant with a comparison with the full population as the result of the small difference in accrual time (1 month). Therefore, no analyses of the bevacizumab

monotherapy arm versus concurrently enrolled patients in the other two treatment arms are provided.

- Progression-free survival: 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 EPP patients.
- Advanced disease status at registration was collected on the E3200 On-Study Form. ECOG indicated to Genentech that ECOG considered this variable unreliable for analysis as collected in this study (telecommunication); therefore, this variable was not included in any analysis. Related information was provided by the prior treatment history information collected through the E3200 Eligibility Checklist. Therefore, this variable was summarized.
- An additional safety analysis was performed in which the incidence of adverse events reported

Appendix 2

Changes in adverse event reporting requirements and the ASEAL with each protocol addendum:

Addendum 3

Changes in reporting requirements

Revised 2/05, Addendum #3

Table 5.26

Expedited reporting requirements for adverse events experienced by patients on study arm(s) who have received at least one dose of Bevacizumab and Oxaliplatin in this study (Arms A, B, and C)

Attribution	Grade 2	Grade 3		Grade 4		Grade 5[b]		Protocol Specific Requirements/ Exceptions
	Unexpected	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected	See footnote (c) for special requirements. See footnote (d) for special exceptions.
Unrelated or Unlikely	[redacted]	AdEERS if Hospitalized	AdEERS if Hospitalized	24-Hr Report and AdEERS	AdEERS	24-Hr Report and AdEERS	AdEERS	
Possible, Probable, Definite	AdEERS[a]	AdEERS[a]	AdEERS if Hospitalized					

24-Hr Report: Please complete a 24 Hour Notification Report via the NCI AdEERS website (http//ctep.cancer.gov/reporting/adeers/html). Please copy ECOG.

AdEERS: Indicates an expedited report is to be submitted within 7 working days of learning of the event.

Hospitalization: Any grade 3, 4, or 5 adverse event which precipitates a hospitalization lasting ≥ 24 hours or prolongs hospitalization must be submitted via AdEERS within 7 working days of learning of the event, regardless of requirements of the study phase, grade, the attribution, or whether the event is expected or unexpected.

a AdEERs reporting is only required if the event is related to the investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

b This includes all deaths within 30 days of the last dose of treatment with an investigational agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with an investigational agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported via AdEERS.

c Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited monitoring for this trial:

Hospitalization: Any grade 1 or 2 adverse event which precipitates a hospitalization lasting ≥ 24 hours or prolongs hospitalization must be submitted via AdEERS within 7 working days of learning of the event, regardless of requirements of the study phase, grade, the attribution, or whether the event is expected or unexpected.

Hemorrhagic Events: Any grade 3-5 hemorrhagic event requires a 24 Hour Notification Report and an AdEERS report within 7 days of learning of the event, regardless of attribution

Hemolysis: Any grade 3-5 hemolysis event with any grade renal failure requires an AdEERS report within 7 days of learning of the event, regardless of attribution

d For study arm A, the adverse events listed below do not require expedited reporting via AdEERS, including hospitalization for these events:

- Grade 1-4 Stomatitis/pharyngitis
- Grade 1-4 Fever without neutropenia
- Grade 1-4 Infection without neutropenia
- Grade 1-4 Headache
- Grade 1-4 Thrombosis/Embolism

For study arm B, the adverse events listed below do **not** require expedited reporting via AdEERS, **including hospitalization for these events:**

* Grade 1-4 Constipation, Ileus, or Bowel obstruction
* Grade 1-4 Dehydration
* Grade 1-4 Diarrhea with and without colostomy and associated electrolyte imbalances
* Grade 1-4 Mucositis, esophagitis, stomatitis/pharyngitis, dysphagia
* Grade 1-4 Nausea or vomiting
* Grade 1-4 Febrile neutropenia
* Grade 1-4 Fever without neutropenia
* Grade 1-4 Infection with or without neutropenia or infection with unknown ANC
* Grade 1-3 Hand/foot skin reaction
* Grade 1-4 Pain -all types including abdominal pain/cramping
* Grade 1-4 Sensory neuropathy
* Grade 1-4 SGOT/SGPT
* Grade 1-4 Thrombosis/Embolism
* Grade 1-4 Fatigue (lethargy, malaise, asthenia)
* Grade 1-4 Neutrophils, leukocytes, hemoglobin, platelets

Addendum 5

Changes in reporting requirements

d For study arm A, the adverse events listed below do **not** require expedited reporting via AdEERS, **including hospitalization for these events:**

* Grade 1-4 Stomatitis/pharyngitis
* Grade 1-4 Fever without neutropenia

Rev. 5/03

* Grade 1-4 Headache
* Grade 1-4 Thrombosis/Embolism

For study arm B, the adverse events listed below do **not** require expedited reporting via AdEERS, **including hospitalization for these events:**

Rev. 5/03

*
* Grade 1-4 Dehydration
* Grade 1-4 Diarrhea with and without colostomy and associated electrolyte imbalances
* Grade 1-4 Mucositis, esophagitis, stomatitis/pharyngitis, dysphagia
* Grade 1-4 Nausea or vomiting
* Grade 1-4 Febrile neutropenia
* Grade 1-4 Fever without neutropenia

Rev. 5/03

* Grade 1-3 Hand/foot skin reaction
* Grade 1-4 Pain -all types including abdominal pain/cramping
* Grade 1-4 Sensory neuropathy

Rev. 5/03

* Grade 1-4 Thrombosis/Embolism
* Grade 1-4 Fatigue (lethargy, malaise, asthenia)
* Grade 1-4 Neutrophils, leukocytes, hemoglobin, platelets

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Addendum 6
Updated ASEAL

Department of Health & Human Services

Public Health Service
National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

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Agent Specific Adverse Events (CTC v2.0)

NSC: 266046 Agent Name: OXALIPLATIN

CTCAE Category	Adverse Events	Other Specify	Comments
ALLERGY/IMMUNOLOGY	Allergic reaction/hypersensitivity (including drug fever)		
AUDITORY/HEARING	Inner ear/hearing		
	Middle ear/hearing		
BLOOD/BONE MARROW	Hemoglobin		
	Hemolysis (e.g., immune hemolytic anemia, drug related hemolysis, other)		
	Leukocytes (total WBC)		
	Neutrophils/granulocytes (ANC/AGC)		
	Platelets		
CARDIOVASCULAR (ARRHYTHMIA)	Sinus tachycardia		
	Supraventricular arrhythmias (SVT/atrial fibrillation/flutter)		
	Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia)		
CARDIOVASCULAR (GENERAL)	Edema		
	Hypertension		
	Phlebitis (superficial)		
	Thrombosis/embolism		
COAGULATION	DIC (disseminated intravascular coagulation)		
CONSTITUTIONAL SYMPTOMS	Fatigue (lethargy, malaise, asthenia)		
	Fever (in the absence of neutropenia, where neutropenia is defined as AGC<1.0 x 10e9/L)		
	Weight loss		
DERMATOLOGY/SKIN	Alopecia		
	Hand-foot skin reaction		

Department of Health & Human Services

Public Health Service
National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

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Agent Specific Adverse Events (CTC v2.0)

NSC: 266046 Agent Name: OXALIPLATIN

CTCAE Category	Adverse Events	Other Specify	Comments
DERMATOLOGY/SKIN	Rash/desquamation		
ENDOCRINE	Hot flashes/flushes		
GASTROINTESTINAL	Anorexia		
	Ascites (non-malignant)		
	Constipation		
	Dehydration		
	Diarrhea patients with a colostomy		
	Diarrhea patients without colostomy		
	Dysphagia, esophagitis, odynophagia (painful swallowing)		
	Gastrointestinal-Other (Specify,____)	Enteritis	
	Gastrointestinal-Other (Specify,____)	Intestinal obstruction	
	Ileus (or neuroconstipation)		
	Nausea		
	Stomatitis/pharyngitis (oral/pharyngeal mucositis)		
	Taste disturbance (dysgeusia)		
	Vomiting		
HEMORRHAGE	CNS hemorrhage/bleeding		
	Hemoptysis		
	Hemorrhage-Other (Specify,____)	Hemorrhage, GU NOS	
	Hemorrhage-Other (Specify,____)	Hemorrhage, Pulmonary/Upper Respiratory Tract NOS	
	Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia		
	Melena/GI bleeding		
	Rectal bleeding/hematochezia		

NSC: 266046 Agent Name: OXALIPLATIN

CTCAE Category	Adverse Events	Other Specify	Comments
HEPATIC	Alkaline phosphatase		
	Bilirubin		
	GGT (Gamma-Glutamyl transpeptidase)		
	Hepatic enlargement		
	SGOT (AST) (serum glutamic oxaloacetic transaminase)		
	SGPT (ALT) (serum glutamic pyruvic transaminase)		
INFECTION/FEBRILE NEUTROPENIA	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10e9/L, fever >=38.5 degrees C)		
	Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10e9/L)		
	Infection with unknown ANC		
	Infection without neutropenia		
METABOLIC/LABORATORY	Acidosis (metabolic or respiratory)		
	Hyperuricemia		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		
	Hypophosphatemia		
MUSCULOSKELETAL	Musculoskeletal-Other (Specify,_____)	Involuntary muscle contractions	
NEUROLOGY	Ataxia (incoordination)		
	Insomnia		
	Mood alteration-depression		

Department of Health & Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

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Agent Specific Adverse Events (CTC v2.0)

NSC: 266046 Agent Name: OXALIPLATIN

CTCAE Category	Adverse Events	Other Specify	Comments
NEUROLOGY	Neuropathy - cranial		
	Neuropathy-sensory		Including acute laryngo-pharyngeal dysesthesias, hyporeflexia, Lhermitte's sign, Paresthesia.
	Vertigo		
OCULAR/VISUAL	Conjunctivitis		
	Ocular/Visual-Other (Specify,___)	Cold-induced transient visual abnormalities	
	Ocular/Visual-Other (Specify,___)		
PAIN	Abdominal pain or cramping		
	Arthralgia (joint pain)		
	Bone pain		
	Chest pain (non-cardiac and non-pleuritic)		
	Headache		
	Myalgia (muscle pain)		Including cramps and leg cramps
PULMONARY	Cough		
	Dyspnea (shortness of breath)		
	Hiccoughs (hiccups, singultus)		
	Pneumonitis/pulmonary infiltrates		
	Pulmonary fibrosis		
	Pulmonary-Other (Specify,___)		
RENAL/GENITOURINARY	Creatinine		
	Renal failure		
	Urinary retention		

Addendum 7
Update to ASEAL

Department of Health & Human Services

Public Health Service
National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

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Agent Specific Adverse Events (CTC v2.0)

NSC: 266046 Agent Name: OXALIPLATIN

CTCAE Category	Adverse Events	Other Specify	Comments
ALLERGY/IMMUNOLOGY	Allergic reaction/hypersensitivity (including drug fever)		
AUDITORY/HEARING	Inner ear/hearing		
	Middle ear/hearing		
BLOOD/BONE MARROW	Hemoglobin		
	Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)		
	Leukocytes (total WBC)		
	Neutrophils/granulocytes (ANC/AGC)		
	Platelets		
CARDIOVASCULAR (ARRHYTHMIA)	Sinus tachycardia		
	Supraventricular arrhythmias (SVT/atrial fibrillation/flutter)		
	Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ventricular tachycardia)		
CARDIOVASCULAR (GENERAL)	Edema		
	Hypertension		
	Phlebitis (superficial)		
	Thrombosis/embolism		
COAGULATION	DIC (disseminated intravascular coagulation)		
CONSTITUTIONAL SYMPTOMS	Fatigue (lethargy, malaise, asthenia)		
	Fever (in the absence of neutropenia, where neutropenia is defined as AGC<1.0 x 10e9/L)		
	Weight loss		
DERMATOLOGY/SKIN	Alopecia		
	Hand-foot skin reaction		
	Injection site reaction		

Department of Health & Human Services

Public Health Service
National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

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Agent Specific Adverse Events (CTC v2.0)

NSC: 266046 Agent Name: OXALIPLATIN

CTCAE Category	Adverse Events	Other Specify	Comments
HEPATIC	Alkaline phosphatase		
	Bilirubin		
	GGT (Gamma-Glutamyl transpeptidase)		
	Hepatic enlargement		
	SGOT (AST) (serum glutamic oxaloacetic transaminase)		
	SGPT (ALT) (serum glutamic pyruvic transaminase)		
INFECTION/FEBRILE NEUTROPENIA	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10e9/L, fever >=38.5 degrees C)		
	Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10e9/L)		
	Infection with unknown ANC		
	Infection without neutropenia		
METABOLIC/LABORATORY	Acidosis (metabolic or respiratory)		
	Hyperuricemia		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		
	Hypophosphatemia		
MUSCULOSKELETAL	Musculoskeletal-Other (Specify _____)	Involuntary muscle contractions	
NEUROLOGY	Ataxia (incoordination)		
	Insomnia		
	Mood alteration-depression		

Department of Health & Human Services — Public Health Service, National Institutes of Health, National Cancer Institute, Bethesda, Maryland 20892

Run by: ADEERSREPORT
Date: 04/05/2004 11:30 AM

Agent Specific Adverse Events (CTC v2.0)

NSC: 266946 Agent Name: OXALIPLATIN

CTCAE Category	Adverse Events	Other Specify	Comments
NEUROLOGY	Neuropathy - cranial		
	Neuropathy-sensory		Including acute laryngo-pharyngeal dysesthesias, hyporeflexia, Lhermitte's sign, Paresthesia.
	Vertigo		
OCULAR/VISUAL	Conjunctivitis		
	Ocular/Visual-Other (Specify,___)	Cold-induced transient visual abnormalities	
	Ocular/Visual-Other (Specify,___)		
PAIN	Abdominal pain or cramping		
	Arthralgia (joint pain)		
	Bone pain		
	Chest pain (non-cardiac and non-pleuritic)		
	Headache		
	Myalgia (muscle pain)		Including cramps and leg cramps
PULMONARY	Cough		
	Dyspnea (shortness of breath)		
	Hiccoughs (hiccups, singultus)		
	Pneumonitis/pulmonary infiltrates		
	Pulmonary fibrosis		
	Pulmonary-Other (Specify,___)		
RENAL/GENITOURINARY	Creatinine		
	Renal failure		
	Urinary retention		

Addendum 8

Changes to ASEAL as follows:

Addendum #8 includes the following changes: 1. Deleted references to the Agent-Specific Adverse Event List; replaced with Comprehensive Adverse Events & Potential Risks (CAEPR) list in "Adverse Event Reporting Requirements" (Sec 5.2.2, pg 14).

Rev. 4/05 * **Arm A and B** - the current NCI Comprehensive Adverse Event and Potential Risks (CAEPR) list for the investigational agent(s) or package insert/protocol for the commercial agents

Rev. 4/05 * **Arm C** - the current NCI Comprehensive Adverse Event and Potential Risks (CAEPR) list

Rev. 4/05 NOTE: The NCI CAEPR is included in Appendix VIII of the protocol To view the most up to date list, please go to the Adverse Event- AdEERS link on the ECOG webpage (www.ecog.org)

Note that additional changes may have occurred to the ASAEL later renamed the CAEPR as this is an online updated list and the changes to the list may not be adequately captured by the protocol addendums.

Appendix 3

Compilation of correspondence and meeting minutes

Our Reference: BB-IND 7921

Division of Cancer Treatment and Diagnosis, NCI
Attention: Dale Shoemaker, Ph.D.
Chief, Regulatory Affairs Branch
Executive Plaza North, Suite 7111
6130 Executive Boulevard, MSC 7428
Bethesda, MD 20892

Dear Dr. Shoemaker:

Please refer to your **Investigational New Drug Application (IND)** for "Bevacizumab [Humanized Monoclonal antibody (rhuMAb VEGF) (Genentech) to the Vascular Endothelial Growth Factor (VEGF)], G-CSF, Peg-interferon alfa-2b, Interferon alfa-2b, and Chemotherapy." We have reviewed the July 25, September 28, and December 7, 2001, and August 22, and September 13, 2002, submissions which contained a new protocol, E3200, "Phase III Trial of Bevacizumab, Oxaliplatin, Fluorouracil and Leucovorin versus Oxaliplatin, Fluorouracil and Leucovorin versus Bevacizumab Alone in Previously Treated Patients with Advanced Colorectal Cancer," and subsequent revisions to study E3200. 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.

We have reviewed this protocol with respect to its ability to provide definitive conclusions as to the use of Bevacizumab in combination with oxaliplatin, 5-fluorouracil, and leucovorin. In its present form, study E3200 is inadequate in design to serve as one of several studies intended to support licensure or a new indication for the treatment of metastatic colorectal cancer. We have the following comments regarding deficiencies in study design that preclude use of the study results for this purpose:

1. The proposed statistical analysis plan lacks an adequate level of detail regarding the prespecified analyses and in some areas, where detail is sufficient, the proposed plan is unacceptable for the purposes of a study intended to support licensure or a new labeling claim. Please address the following comments:

a. The population in which the primary efficacy analysis will be performed is unclear. Please confirm that the primary analysis will utilize the intent-to-treat population.

b. It appears that you plan to use a logrank test in the primary analysis. Please clarify whether this analysis will employ the stratification factors used during randomization. Please provide an analysis plan that incorporates the change in stratification factors, i.e. the removal of measurable disease as a factor during the study accrual period.

c. Please revise the protocol to discuss how to conserve the overall alpha level due to the interim analyses and the multiple comparisons. Please provide a significance level and/or boundary for each of the interim analyses and for the final analysis.

e. Please clearly state the number of events that will be examined in the final analysis of the primary endpoint.

f. Please incorporate the definitions for overall survival and progression free survival in the Statistical Considerations section.

g. Please include the censoring of patients who are lost to follow-up in the analysis of overall survival and progression free survival in the Statistical Considerations section. In addition, please provide the methods that will be employed to obtain survival data in patients who are lost to follow-up.

h. As currently designed, this study will enroll first, second, and third line patients, but fails to stratify for this factor. During the study analysis, please examine an imbalance in this factor.

i. Please note that the primary and secondary objectives do not correspond to those outlined in the Statistical Considerations section. Please revise the section of the protocol entitled Objectives to be consistent with the section entitled Statistical Considerations. The primary and secondary efficacy objectives of the study should be clearly identified and consistently stated in these two sections.

j. In the analysis of secondary endpoints, please provide a discussion of the manner in which the following patients will be handled in the statistical analysis:

   1) Patients on Arm A who continue on study, but have discontinued either Bevacizumab or oxaliplatin/5-fluorouracil/leucovorin for toxicity.

   2) Patients on Arm B who are removed from study and have discontinued oxaliplatin/5-fluorouracil/leucovorin for toxicity.
   3) Patients on Arm C who are removed from study and have discontinued Bevacizumab for toxicity.

We recommend that patients on each arm be defined as "removed from study", that is, removed from active treatment, using consistent criteria across study arms, because

patients who are removed from study will undergo disease assessments at intervals different from those mandated on study. In the absence of a consistent approach to assessment of disease progression (i.e., consistent interval and manner of evaluation for disease status) across study arms, the analysis of disease-free survival will be considered biased and unacceptable for use in support of licensure or a new labeling claim.

k. Please present a plan to assess for and quantitate the degree of bias introduced by the lack of blinding in this study. This plan should include an analysis of early discontinuation in Arms B and C. In the absence of an analysis that suggests the absence of bias in study conduct, the study will be considered unacceptable for use in support of licensure or a new labeling claim.

l. We strongly recommend that you incorporate a sensitivity analysis that examines the effect of inclusion criteria added during study enrollment, such as the effect of the accrual of patients who have failed adjuvant 5-fluorouracil/leucovorin/irinotecan.

2. We have the following comments concerning aspects of the study that appear to increase the risks to subjects and have not been adequately justified in the protocol. If the safety data are insufficient to characterize the toxicity profile of Bevacizumab or if the trial design resulted in unreasonable risks to patients, the results of this study may be unacceptable for support of licensure for these reasons as well as those cited above. Please address the following comments and requests for information:

a. The criteria for the dose reduction of oxaliplatin should be similar to those in the package insert. You have not provided data to justify the safety of alternate criteria.

b. You have not provided data to justify the inclusion of patients with a history of uncontrolled congestive heart failure, regardless of the time interval. Please provide justification for this inclusion criterion and describe how the safety of enrollment of patients with a history of congestive heart failure is being actively monitored and evaluated during the conduct of the study to ensure that increased risks in such patients will be identified as early as possible in the course of the study.

c. Patients who discontinue due to a serious adverse event should be followed for resolution. Patients with certain target adverse events known to be associated with Bevacizumab and of lower grade should also be followed for resolution. Please confirm that, although not specifically stated in the protocol, the investigators in this study are following all patients with evidence of serious and treatment-related toxicities (e.g., proteinuria) to resolution.

d. The study should provide specific recommendations for the treatment of diarrhea. In the absence of specific recommendations, you should collect information on concomitant medications and perform analyses to assess the effectiveness of various interventions.

e. Please clarify whether the Data Monitoring Committee (DMC) will review the incidence and severity of cardiac events, hypertension, and bowel perforation. If not, confirm that such assessments will be specifically incorporated in the DMC charter.

f. Please submit copies of the short summary reports for the toxicity reviews conducted by the DMC. These reports should include all serious adverse events and all Grade 3 and 4 adverse events, regardless of the relationship to the study drug.

g. Please provide evidence for the value of a reduction in the dose of Bevacizumab in patients with coagulopathy or hypertension. Alternatively, please revise the analytic plan to address this important question.

We have the following additional comments that do not directly affect the acceptability of this study for the purposes of licensure or supporting a new labeling claim:

3. Please examine the use of prior infusional 5-fluorouracil or capecitabine in the study analysis.

4. Please collect serum chemistries in order to provide an accurate assessment of the toxicity profile of this regimen as reflected by changes in serum chemistries.

5. In the datasets and safety analyses, please distinguish the adverse events collected from the patient diary from those collected by patient interview.

6. Please collect blood pressure measurements with each dose of Bevacizumab.

7. In the entry criteria and in the section concerning the use of concomitant medication, we recommend that you prohibit the use of non-steroidal anti-inflammatory agents in doses that would inhibit platelet function.

8. The patient diaries used in this study are very complicated and we believe that many patients would be unable to complete these diaries. Please provide evidence of the ability of patients to adequately complete these diaries.

9. We have the following comments regarding the informed consent document:

   a. Please clarify why congestive heart failure is not included in the informed consent and in the list of Bevacizumab specific adverse events in Appendix VIII.

   b. Please provide the criteria for designating events as rare, less likely, or very likely.

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 827-5101.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Our Reference: BB-IND 7023

Genentech, Incorporated
Attention: Robert L. Garnick, Ph.D.
Senior Vice President, Quality, Regulatory Affairs and Corporate Compliance
1 DNA Way, MS #242
South San Francisco, CA 94080

Dear Dr. Garnick:

We have reviewed the July 1, 2005, submission to your **Investigational New Drug Application (IND)** for "Bevacizumab [Humanized Monoclonal Antibody (rhuMAb VEGF) to the Vascular Endothelial Growth Factor] and Chemotherapy," which contained a revised plan for submission of a supplemental Biologics License Application (sBLA) for expansion of product labeling to include the second-line treatment of metastatic colorectal cancer. We also refer to the March 10, 2005, teleconference, between representatives of Genentech and this office in which this sBLA was discussed.

With regard to the questions posed in your July 1, 2005, submission, we have the following responses:

1. Does the Agency agree with Genentech's revised proposal for the contents of the sBLA, including the Clinical Study Report, patient narratives, Case Report Forms, and Case Report Tabulations?

   FDA Response: We do not agree with your revised proposal. The July 1, 2005, proposal differs substantially from that agreed to during the March 10, 2005, teleconference. A detailed comparison of the original agreement, your proposed revisions, and FDA's assessment of the changes are provided in Attachment 1. With regard to your July 1, 2005, proposal, we request that the following additional data be included in the proposed supplement:

   a. Patient narratives for the following targeted adverse events occurring in the Bevacizumab-treatment arm:

      1) NCI-CTC Grades 3 or 4 congestive heart failure;

      2) NCI-CTC Grades 3 and 4 proteinuria;

      3) NCI-CTC Grade 4 hypertension; and,

      4) NCI-CTC Grade 3 and 4 intra-abdominal abscess.

   b. A listing, by patient ID, of all adverse events occurring within 30 days of study drug discontinuation for each patient in the Bevacizumab arm who discontinued treatment for toxicity.

c. The proposal to provide narrative descriptions of adverse events for only those patients in the experimental arm is acceptable. Please be aware that this 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 considered attributable to Bevacizumab because there will be insufficient information on background event rates in the control arm to permit any other conclusion.

d. For Protocol E3200, please provide the case report forms for patients in the control arm who have experienced the following: death, discontinuation of study treatment, perforation, fistula, arterial thromboembolism, and Grade 3-4 events. In addition, please make case report forms for any patient available upon request by FDA during the course of the review.

e. Please incorporate information from all available sources in the narrative summaries of adverse events, including both the AdEERs and the clinical database. Please highlight discrepancies in the information provided in these two databases. Discrepancies may include adverse events that were included in one database and not the other or discrepancies in the data associated with the event (such as laboratories or adverse events associated with the primary event).

Prior to the submission of the sBLA, we request that you provide additional information (such as mock up tables or listings) concerning the display of these discrepancies for our review and comment.

f. Please insert a flag in the safety and efficacy datasets to identify those patients requiring dose modifications.

g. Please provide the programs that were used to create the derived datasets from the raw datasets in the sBLA. 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.

h. We do not object to the inclusion of exploratory analyses which compare patients in the Bevacizumab alone arm to all patients in the FOLFOX4 and the FOLFOX4 plus Bevacizumab arm (rather than the subset of patients enrolled during the period when all three study arms were open to accrual). However, we do not accept the validity of your approach. Please include flags in your datasets which identify patients enrolled during the period when all three study arms were open to accrual.

i. You stated that, "The ECOG database will provide the most current and complete safety and efficacy information available at the time of the sBLA submission." You also stated that, "The analyses presented in the E3200 CSR will be based on the database judged by ECOG to provide valid inference for this study." Please clarify the meaning of these statements concerning the completeness of the database.

2. Does the Agency agree with Genentech's revised proposal for the Summaries of Clinical Efficacy and Safety?

   FDA response: We do not agree with all of the proposed revisions. A detailed comparison of the original agreement, your proposed revisions, and FDA's assessment of the changes are provided in Attachment 2. With regard to your July 1, 2005, proposal, we have the following comments and requests for additional data:

   a. Please include integrated safety analyses for intra-abdominal abscesses and fistula formation along with other selected adverse events in the Summary of Clinical Safety.

   b. Please submit documentation of due diligence in collection of financial disclosure information for investigators prior to March 2002.

   c. Please note that the absence of the information typically supplied in the Summaries of Clinical Safety and Efficacy may make review of the application less efficient.

We also have the following additional requests for information to be provided in the proposed supplemental application:

3. The following information, captured on the eligibility checklist, should be provided in the electronic datasets.

   a. First line therapy;

   b. Baseline dipstick and 24 hour urine results;

   c. History of hypertension and whether hypertension was considered by the investigator to be well controlled;

   d. Days from last major surgical procedure prior to entry;

   e. Use of aspirin, anti-platelet agents, or therapeutic anticoagulation prior to entry; and,

   f. History of myocardial infarction, congestive heart failure, or unstable angina within three months of entry.

4. The presence and type of protocol violations should be included as a data variable in the efficacy and safety datasets. This should include flags for both eligibility violations such as no prior 5-fluorouracil and/or irinotecan, prior oxaliplatin, history of thrombosis, and history of hemorrhage, and for protocol treatment violations, such as deviations from protocol-prescribed treatment plan including dose modifications.

The following comments relate to your proposed supplements to expand the Avastin labeling to include treatment of [redacted] b(4)

5. Please submit the eligibility checklists (if used) for Protocols ——————— so that we may determine the need for data from these checklists in the sBLA submissions. b(4)

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) 827-5101.

Sincerely yours,

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

ATTACHMENT 1

	Previous Agreement	Revised Proposal	FDA Requests
Narratives	• Death • Bevacizumab d/c or dose modification • Perforation, fistula • Arterial TE • AdEERs Gr 3-4 events • Gr 3-4 hemorrhage • Gr 3-4 venous thrombosis • Gr 3-4 CHF • Gr 3-4 proteinuria • Gr 4 HTN • Gr 4 diarrhea • Gr 3-4 sensory neuropathy • Second malignancies	• Death • D/c of study Rx • Perforation, fistula • Arterial TE • AdEERs Gr 3-4 events • Gr 3-4 hemorrhage • Gr 3-4 sensory neuropathy • Second malignancies • Gr 3-4 post-op complications	In addition, please include narratives for • Gr 3-4 CHF • Gr 3-4 proteinuria • Gr 4 HTN
Narratives	Study Discontinuation	[redacted]	Please list all AEs within 30 d of discontinuation by patient number. b(4)
Narratives	All 3 arms	Only pts who received Bevacizumab	Agree
	Pts who require narratives	[redacted]	• Please submit CRFs for all patients (all 3 arms) who, based on the criteria above, require narratives. • All CRFs should be available on request. b(4)
Analyses	Per SAP	• No subgroup analysis for PFS, RR • No multivariate analysis of PFS, RR	Agree
Analyses	Comparison of pts concurrently enrolled in all 3 arms	Comparison of Bevacizumab arm w/all pts in other 2 arms	We do not object to the inclusion of this exploratory analysis. However, FDA does not accept the validity of your approach.
CSR		Only hemorrhage, N/V, HTN, arterial TE, sensory neuropathy, perforation by age, sex, race, PS	Please include abdominal abscess and fistula formation with perforation.

ATTACHMENT 1 (CONT)

	Previous Agreements	GNE revised proposal	FDA requests

AdEERs		• AEs reported to AdEERs summarized by arm. • AdEERs presented separately from CRF collected toxicity	Differences between the AEs collected by AdEERs and the CRFs should be highlighted.
Bevacizumab Dose Modification		AEs leading to dose modification summarized	Agree. Please provide a flag in the database to identify pts who have had a dose modification.
SAS Datasets	• E3200 • Integrated single agent	[redacted]	• Programs for 1^0 and 2^0 analyses. • Programs for creating the derived datasets.

b(4)

ATTACHMENT 2

	Previous	Revised	FDA Requests
CSRs	• E3200 • AVF2107g • TRC-0301	• E3200 • AVF2107g • TRC-0301 • AVF2192g • AVF0780g	Agree
SCS	• E3200 • Integrated SCS in BLA	• Cross reference E3200 CSR • CSR will include safety results from GNE CRC studies for perforation, HTN, proteinuria, arterial TE, hemorrhage, N/V/D, sensory neuropathy	Please include intra-abdominal abscess and fistula.
SCS	Pooled single agent data	No	FDA will perform these analyses for selected AEs.
SCS		CSR for E3200 will include Gr 3-5 non-hematologic, Gr 4-5 hematologic AEs by age, sex, race	Agree
SCE	• E3200 • AVF2107g • AVF2192g • AVF0780g • Not integrated	Cross reference E3200 CSR	Agree
Financial Disclosure		Financial disclosure forms submitted after 3-02	Please provide evidence of due diligence in the collection of financial disclosure information prior to 3-02.

Our Reference: BB-IND 7023

Genentech, Incorporated
Attention: Robert L. Garnick, Ph.D.
Senior Vice President, Quality, Regulatory Affairs and Corporate Compliance
1 DNA Way, MS #242
South San Francisco, CA 94080

Dear Dr. Garnick:

We have reviewed the April 13, 2005, submission to your **Investigational New Drug Application (IND)** for "Bevacizumab [Humanized Monoclonal Antibody (rhuMAb VEGF) to the Vascular Endothelial Growth Factor (VEGF)] and Chemotherapy." This submission contained a plan to integrate adverse event information in patients treated with single agent Bevacizumab in study E3200, "Phase III Trial of Bevacizumab, Oxaliplatin, Fluorouracil and Leucovorin versus Oxaliplatin, Fluorouracil and Leucovorin versus Bevacizumab Alone in Previously Treated Patients with Advanced Colorectal Cancer" with single agent Bevacizumab adverse event information in Genentech's database. We have completed our review of your submission and find your plan acceptable.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 827-5101.

Sincerely yours,

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

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

Memorandum

Date: April 5, 2005

From: Sharon Sickafuse, CDER/ODE6/DRMP

To: IND 7023

Subject: March 10, 2005, pre-sBLA teleconference with Genentech regarding ECOG study E3200

Teleconference Date: March 10, 2005

Teleconference Requestor: Genentech, Inc.

Product: Bevacizumab

Proposed Use: Treatment of colorectal cancer

Teleconference Purpose: Discuss proposed content of sBLA for ECOG study E3200, "Phase 3 Trial of Bevacizumab, Oxaliplatin, 5FU, and Leucovorin versus Chemotherapy Alone Versus Bevacizumab Alone in Previously Treated Patients with Advanced Colorectal Cancer. Teleconference package is amendment 523.

Background: Draft FDA responses to Genentech's questions were faxed to Genentech on March 2, 2005. Genentech's questions, FDA draft responses, and discussion between FDA and Genentech are captured below.

1. *Based on the significant survival results and the safety profile observed with bevacizumab in Study E3200, Genentech believes that the results from this pivotal trial are sufficient to support an sBLA to extend the current indication of Avastin to the following:*

b(4)

Does the Agency agree that Study E3200 can form the basis for this sBLA? Does the Agency agree with the proposed indication statement?

FDA Response:

- The Agency cannot comment upon the indication statement prior to review of the primary data.

- Data from AVF2107g (1st line), E3200 (2nd line), and ——— will be used in the evaluation of this indication. b(4)

Discussion:
Genentech stated that they will provide in the sBLA clinical study reports for 2107g and E3200 and a summary report from NCI on study ——— b(4)

2. *Does the Agency agree with Genentech's proposal for submission of the clinical study report, patient narratives, case report forms, and case report tabulations?*

FDA Response: No. Please see the following table:

	GNE Proposal	FDA
CRFs	Pts w/narratives	Pts w/narratives
Narratives	Deaths < 30 d not due to PD, related deaths > 30 d. AEs leading to discontinuation AEs leading to dose reduction GI perforation, fistula formation Arterial events Gr 4 Events-proteinuria, HTN, diarrhea Gr 3-4 Events-venous thrombosis, CHF, hemorrhage, abn healing or bleeding AdEERs Reports	Please include Gr 3 proteinuria. Please include patients with second malignancies. Please include Gr 3 and 4 neuropathy leading to discontinuation of oxaliplatin.
Safety Update	None	Pts currently on study included in initial data submission (see item 6)

- Please confirm that narratives will be provided for approximately 40% of patients.
- Please state the availability of dosing and dose modification information.
- We acknowledge that pharmacokinetic information will not be provided.
- Please confirm that all protocols, protocol amendments, data monitoring committee charter(s), data monitoring committee minutes and analyses, statistical analysis plans, and amendments to the statistical analysis plan will be submitted.

Discussion:
FDA inquired about the relationship between AdEERs reports and patient narratives because of a concern that AdEERs narratives are often incomplete. Genentech stated that the patient narrative is drawn from the AdEERs report and the CRF.

Genentech agreed to provide narratives for patients with Grade 3 proteinuria and the patients with a second malignancy (gastric cancer). Genentech and FDA agreed that Genentech would provide narratives for all patients who discontinue oxaliplatin, regardless of cause. Genentech confirmed that narratives will be provided for approximately 40% of patients.

Regarding the issue of dose and dose modification information, ECOG stated that they are collecting dosing information on only those patients who had modifications of the Bevacizumab dose or discontinued Bevacizumab. FDA said this was acceptable and asked Genentech to confirm the other patients had the planned Bevacizumab dose as per protocol.

Genentech confirmed that all protocols, protocol amendments, statistical analysis plans (SAPs), and amendments to the SAPs will be submitted in the sBLA. ECOG stated that they can provide general policies for the data monitoring committee (DMC), but not a specific charter for this study because there isn't one. ECOG clarified that the DMC minutes consist of the topics discussed and the final conclusion, but not the actual discussion that took place. These minutes will be included in the sBLA.

3. *Does the Agency agree with Genentech's proposal for basing the study conclusions for E3200 in the sBLA on two sources (the November 2004 interim analysis results and the analyses presented in the clinical study report) as described in Section 10.1.1?*

FDA Response:

- The study conclusions for E3200 submitted in the sBLA should be those agreed to in the final SAP.
- DMC minutes and analyses should be provided as part of the sBLA.
- Please provide the rationale behind your intent to provide two conclusions.

Discussion:
Genentech confirmed that the study conclusions for E3200 will be based on the analyses in the final SAP. They will provide the DMC minutes as discussed in item 2. Genentech clarified that while they are using two sources for the survival endpoint, information in the sBLA on the November 2004 interim analysis will only state that the results of the interim analysis showed statistical significance.

4. *Does the Agency agree with Genentech's proposals for the Summary of Clinical Efficacy and Summary of Clinical Safety to be provided?*

FDA Response:
No. Please see table below.

	GNE Proposal	FDA
ISS	E3200 Integrated GNE trials-excluding extension studies [redacted]	E3200 Integrated GNE trials-excluding extension studies Integration of GNE & E3200 single agent experience
ISE	E3200 AVF2107g AVF2192g	E3200 AVF2107g AVF2192g AVF0780g

b(4)

In the initial Bevacizumab BLA, information was provided on 157 patients who received single agent therapy. E3200 will provide additional information on 239 patients who received single agent Bevacizumab. Please provide safety analyses for the 239 patients on E3200 as well as an ISS for these 239 patients with the 157 other patients who also received single agent Bevacizumab.

Discussion:
FDA would like to evaluate the toxicity profile of single agent Bevaciuzmab using a larger safety database. This will be facilitated by the integration of the single agent experience in E3200 with other Genentech studies.

FDA also plans to compare the toxicity profile of Bevaciuzmab versus Bevacizumab plus chemotherapy within E3200

Genentech/ECOG expressed reluctance to provide an ISS for the [redacted]. They believe that the most relevant comparison is that of Bevacizumab to Bevacizumab plus chemotherapy within E3200. Genentech agreed to provide a proposal for the integration of the [redacted]

b(4)

In response to an FDA question, ECOG clarified that the adverse event terms used were from the NCI-CTC Version 2. FDA noted that this makes integration easier than if the Genentech studies and the E3200 study used different adverse event terms.

5. *Does the Agency agree with Genentech's plans to submit the application in eCTD format?*

FDA Response: Yes. However, please contact Joseph Montgomery and Gary Gensinger to obtain detailed information concerning the submission. A browser to review the document would be most helpful.

6. *Genentech does not intend to submit a Safety Update to the sBLA. Does the Agency agree?*

FDA Response: As of 12-04, 30 patients were receiving active therapy on Arms A and B. Please include information on deaths, discontinuations, expedited reports, serious adverse events, adverse events, and patient narratives (as appropriate) for these patients as of 6-05 in the sBLA. It is not necessary to integrate this information into your safety analyses.

Discussion: Genentech stated that they are not using 12-04 as the date of database cut-off. The database cut-off will be midsummer, but no exact date has been set. It is likely that there will be no patients on active therapy at that point.

Genentech agreed to provide the requested data if patients are still on active therapy by database cut-off. FDA asked Genentech to highlight any areas in which they could not collect the data.

7. *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*?

FDA Response: Yes.

Additional FDA Comments:

1. When submitting the final study report for E3200, please note in your cover letter that this will address Post-Marketing Commitment 17.

   Genentech will do this.

2. Please provide the eligibility checklist used by ECOG. Please state whether information collected on the checklist will be submitted in the sBLA.

   Genentech agreed to fax the eligibility checklist to Dr. Maher. They were not planning on submitting data from the checklist as part of the sBLA.

3. The On-Study Form (ECOG case report forms) collects information on current tumor sites and prior adjuvant therapy (yes/no). In Attachment E slide 13, you provide

information on the first line and adjuvant therapy received. Please state what information, in addition to that in the case report forms, was collected and what will be included in the sBLA.

Genentech stated that this information was from the eligibility checklist. They will provide a blank checklist. Genentech intends to include only information on first line and adjuvant therapy from this checklist. FDA will review the checklist.

4. Please include information on the extent of study monitoring such as sites monitored, number of visits to each site during conduct of E3200, and the number of E3200 case report forms monitored at each site, by the NCI in the sBLA submission. Do the site monitor reports provide specific information on E3200? Can you provide information on the number of patients on E3200 that were audited?

   ECOG agreed to provide a brief overview. ECOG sites are audited every 36 months. The audit is based on the work of the entire institution of all the protocols they were involved in. NCI stated that they will discuss the extent of study monitoring on cooperative group trials at an upcoming meeting with the FDA.

5. In Table 2, you refer to 41 patients in the Expanded Patient Protocol. Please state whether this refers to patients enrolled by the CTSU. If not, please provide a copy of the Expanded Patient Protocol along with information on its relationship to E3200.

   NCI clarified that "EPP" means Expanded Participation Project. Patients on E3200 were enrolled directly from ECOG. Patients in the EPP were enrolled through the CTSU for other participating cooperative groups. The EPP involves practices which are not affiliated with the cooperative groups. Data from the EPP was submitted electronically and there were slight differences in the data collected from the EPP and the data collected from ECOG and CTSU. Genentech will submit data on these patients as well as an explanation of how these patients' data differs from standard ECOG data collected.

6. Please provide, in the sBLA, additional information on the data that was submitted to members of the Gastrointestinal Intergroup prior the final analysis of E3200 by the DMC.

   ECOG stated that the Gastrointestinal Intergroup made this request to the ECOG for planning purposes. The ECOG DMC reviewed the request and recommended that survival data as of 6-28-04 from arms A and B be provided to four people in the Gastrointestinal Intergroup. These four people signed confidentiality statements.

Issues Requiring Further Discussion:

Presentation of the integrated safety data for [redacted] Bevacizumab.

b(4)

Action Items for Genentech:

1. Provide a proposal for the integration of the [redacted]
2. Fax the ECOG eligibility checklist to Dr. Maher

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
Robert Justice, M.D.
Ellen Maher, M.D.

Office of Biostatistics
Biological Therapeutics Statistical Staff
Mark Rothmann, Ph.D.

Sponsor Attendees:

Genentech, Inc.

Alex Bajamonde, Ph.D., Director, Oncology Biostatistics
Lisa Bell, Ph.D., Manager, Regulatory Affairs
Julie Hambleton, M.D., Associate Director, Medical Affairs
Betty Nelson, M.A., Senior Biostatistican, Medical Affairs
Michelle Rohrer, Ph.D., Director, Regulatory Affairs
Somnath Sarkar
Jamey Skillings, M.D., Group Director, Medical Affairs
Kathleen Winson, Associate Operational Team Leader

ECOG

Robert Comis, M.D., Group Chair
Bruce Giantonio
Robert Gray, Ph.D., Group Statistician
Mary Steele

NCI

Meg Mooney, M.D., Senior Investigator, Clinical Investigations Branch, CTEP, DCTD

University of North Carolina

Richard Goldberg, M.D., Head, Colon Cancer Task Force for GI Intergroup

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

Memorandum

Date: April 7, 2004

From: Sharon Sickafuse, CDER/ODE6/DRMP

To: IND 7023

Subject: March 23, 2004, meeting with Genentech, ECOG, and NCI regarding protocol E3200

Meeting Date: March 23, 2004

Meeting Requestor: Genentech, Incorporated

Product: Bevacizumab [Humanized Monoclonal Antibody to the Vascular Endothelial Growth Factor (VEGF)] and Chemotherapy

Proposed Use: Treatment of colorectal cancer

Meeting Purpose: Discuss FDA's June 5, 2003, letter to NCI (IND 7921) regarding the statistical analysis plan for E3200 "Phase III Trial of Bevacizumab, Oxaliplatin, Fluorouracil and Leucovorin versus Oxaliplatin, Fluorouracil and Leucovorin versus Bevacizumab Alone in Previously Treated Patients with Advanced Colorectal Cancer"

Sponsor Questions and FDA Responses:

1. *Does the FDA concur with the content of the Statistical Analysis Plan (provided in Attachment B) for Study E3200?*

   Does the FDA agree with the primary analysis comparison for duration of survival between Arm A (FOLFOX + bevacizumab) and Arm B (FOLFOX alone) as defined in the Statistical Analysis Plan?

FDA advised Genentech that the Statistical Analysis Plan (SAP) is generally acceptable, however FDA had the following recommendations in order to make the SAP fully acceptable.

- Please provide a clear statement that the analyses as outlined in the SAP supercede those in the protocol.

  Genentech agreed to do so.

- When there is a statistically significant result for the primary analysis of the primary endpoint, claims based on secondary endpoints that are significant after proper (pre-specified) adjustment for the multiplicity of secondary endpoints may be included in the label. Please describe the adjustments that will be made for multiplicity to guarantee an overall 0.05 level for secondary endpoints.

  Genentech stated that they will revise the SAP to correct for multiplicity in secondary endpoints.

- Please provide additional information on the level of difference in censoring patterns for survival in Arms A and B that will trigger an additional analysis and describe the sensitivity analysis(es) that will be performed.

  NCI clarified that they continue follow-up for survival on patients who have refused their treatment assignment or discontinued treatment in the same manner and degree as patients who have accepted their treatment assignment and have very few patients in which they cannot obtain survival information.

  FDA explained that they were concerned about the possibility of bias in this open label study. Examples include patients who refuse assignment or a large number of patients who discontinue due to low-grade toxicity.

  FDA recommended that Genentech propose a series of sensitivity analyses for dealing with missing data, using various imputatations for missing data.

  Genentech acknowledge this request.

- Please provide information on the boundary levels for the interim analyses and the alpha that were used to declare a significant result in these analyses. Only planned interim analyses should be performed with pre-specified alpha adjustments. There should be no unplanned interim analyses. The integrity of the results may be impacted by unplanned analyses.

- FDA noted that the safety information from Arm C will be used in exploratory analyses which compare patients concurrently enrolled on

  Arms A, B, and C. Please provide additional information on the way in which safety information from Arm C will be presented.

  Genentech clarified that safety information from Arm C will be presented in the same way as safety information from Arms A and B is presented. They will compare all arms at the time all arms were open to enrollment.

- Please specify the type of progression (clinical, radiologic, both) that will be included in the analysis of progression free survival. Please provide inclusion of criteria for determination of progression.

  Genentech stated that progression-free survival will be based solely on radiological evidence of disease. Genentech will specify this in the revised SAP.

- The SAP states that one of the objectives is a primary analysis that will consist of a primary comparison between Arms A and B. However, in Section 3.5.1, both a comparison of Arms A and B and three pairwise comparisons are described. FDA considers that the objective and design of the study are determined by the test method (3 pairwise comparisons in which each study arm is considered a "treatment arm"). Please revise the primary objective to be consistent with the statistical plan.

  Genentech agreed to revise the primary objective as stated in the protocol to be consistent with the statistical plan.

2. *With submission of the Statistical Analysis Plan and the responses to the FDA letter dated June 5, 2003, does the FDA agree that Study E3200 is adequate in design to support the proposed expansion of the Avastin label to include use of Avastin for the treatment of patients with* ——————————————— b(4)

FDA stated that there are significant limitations in the rigor and completeness with which data has been collected in this trial. These deficiencies include, but are not limited to:

- Lack of information on the dose of Bevacizumab received. (CRF doesn't capture this.)
- Lack of information on dose modifications of Bevacizumab and subsequent adverse events. For example, if a patient's dose was reduced from 10 mg to 5 mg due to hypertension, how did this dose reduction affect the patient's blood pressure?
- Lack of information to verify patient eligibility. The CRFs don't verify that patients have failed 5FU/irinotecan.

FDA asked Genentech to describe their plan to capture additional data and to audit the existing data.

Genentech and NCI confirmed that information on the dose of Bevacizumab received was not captured. FDA inquired if it was possible to obtain the drug accountability records from the site pharmacists to determine the dose(s) of Bevacizumab that each patient received. NCI stated that they would investigate how labor intensive this might be. Genentech will provide information regarding collection of Bevacizumab dosing data which will be the subject of a follow-up telecon with FDA. FDA stated that information on the dose received will be necessary for labeling.

NCI noted that in general, the protocol required that the dose of Bevacizumab be reduced from 10 mg/kg to 5 mg/kg for Grade 2 events. Only Grade 3-5 adverse events that were thought to be related were collected.

Regarding verification of patient eligibility, ECOG stated that they normally audit 10% of the study sites. For study E3200, 17% of the study sites have been audited; the auditing process includes verification of patient eligibility. Regarding site audits, ECOG audits a site every 3 years, therefore, all sites participating in study E3200 were audited at least once during the conduct of the study, however, because the audits are of study sites, not of specific protocols, the level of auditing of patients enrolled in a specific protocol is unknown.

FDA asked NCI to provide to Genentech the audit report and "grade" for all ECOG sites participating in this trial along with the number of patients enrolled at each of these sites. Genentech will submit the information as an amendment to IND 7023. After review of this information, FDA will comment on whether there are concerns about the conduct of the trial and data validity and determine whether additional auditing is needed and required.

Additional Discussion Items:

The protocol states that two interim analyses will be performed, when 50% and 75% of deaths have occurred. FDA asked if the first interim analysis had occurred yet.

ECOG stated that the first interim analysis has occurred, however the timing of the analysis was not according to the SAP in that it occurred after 50% of deaths (i.e., analysis occurred later than it should have). The draft report for the DMC has been written and will be presented to the DMC on April 26th.

ECOG stated that the date of data cut-off for the first interim analysis occurred in late February. Data-cut-off for the second interim analysis will occur in late August/early September, however a specific date has not yet been set. FDA stated that setting a data cut-off date for the second interim analysis when the specific results of the first interim analysis are known (whether or not statistical significance was reached) will alter the overall type I error rate.

FDA recommended setting the data cut-off date for the second interim analysis at precisely 6 months after the data cut-off date for the first analysis. ECOG agreed to do so.

Action Items

1. ECOG will revise and resubmit the SAP to Genentech so that Genentech can submit as an amendment to IND 7023. The revised SAP must be submitted as an amendment to IND 7023 before the interim analysis results from the first interim analysis are made public.
2. ECOG will set a data cut-off date for the second interim analysis which is exactly 6 months from the data cut-off date for the first interim analysis.
3. NCI will submit site audits to Genentech to that Genentech can submit as an amendment to IND 7023.

4. NCI/CTEP will investigate the feasibility of acquiring site pharmacy records to determine all doses of Bevacizumab that each patient received and entering this information into an electronic database.

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
Patricia Keegan, M.D.
Ellen Maher, M.D.

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

Sponsor Attendees:
Genentech, Incorporated
Alex Bajamonde, Ph.D., Director, Biostatistics
Diana Clark, Ph.D., Project Team Leader
Robert Garnick, Ph.D., Senior V.P., Quality, Regulatory Affairs, and Corporate Compliance
Julie Hambleton, M.D., Clinical Scientist, Medical Affairs
Cathy Sueoka-Lennen
Cheryl Madsen, Senior Manager, Regulatory Affairs
Robert Mass, M.D., Director, Medical Affairs,
Gene Murano, M.D.,
Todd Rich, M.D.,
Beth Rogers, Operations Team Leader, Medical Affairs
Somnath Sarkar, Ph.D., Senior Biostatistician, Oncology Biostatistics

NCI, CTEP, DCTD

Helen Chen, M.D., Senior Investigator, Investigational Drug Branch
Meg Mooney, M.D., Senior Investigator, Clinical Investigations Branch
Larry Rubinstein, Ph.D., Statistician, Biometric Research Branch

ECOG

Bruce Giantonio, Executive Officer and E3200 Study Chair
Robert Grey, Group Statistician

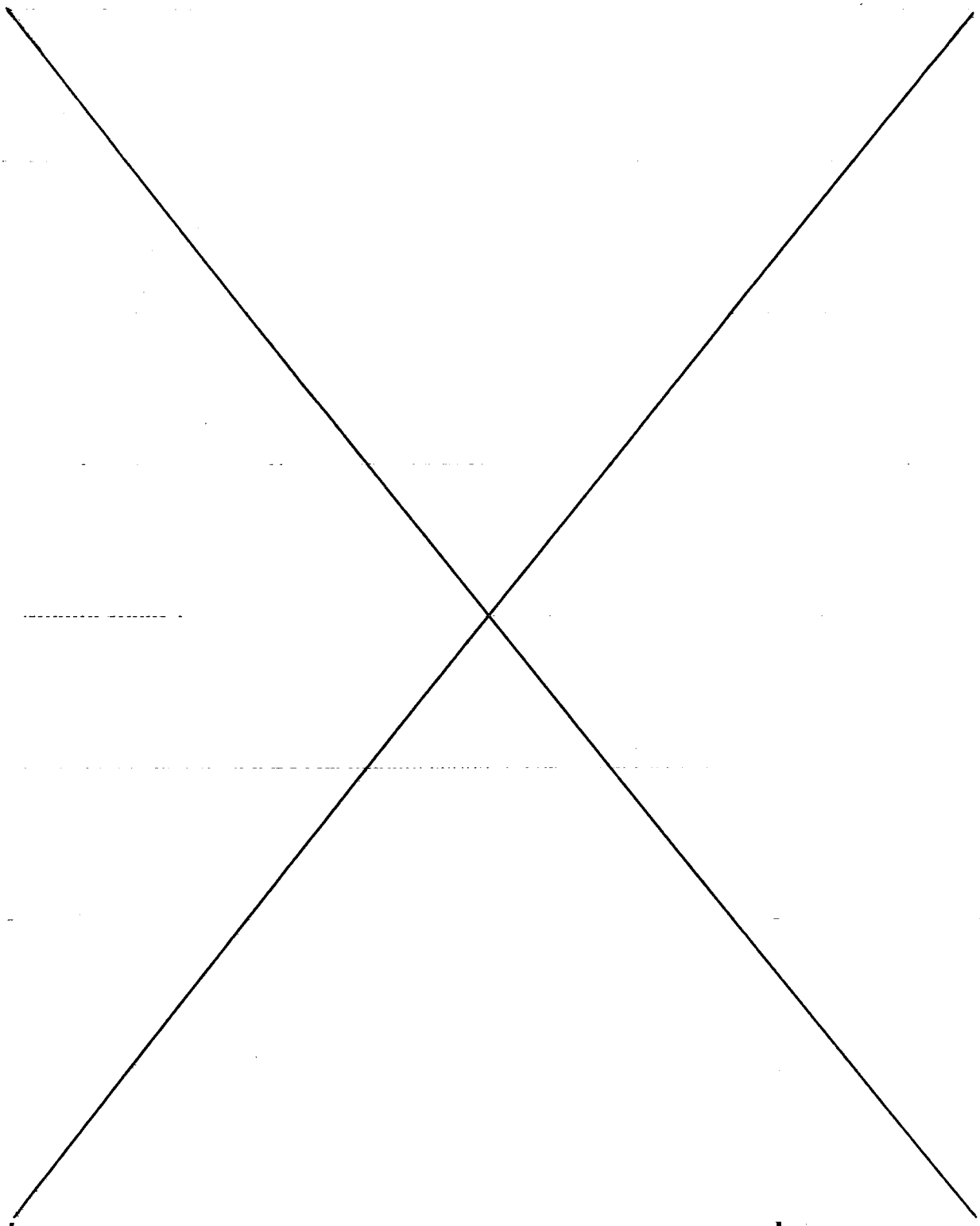
Hoffman-La Roche

Susan Tremlett, Avastin Operations Project Leader

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

1.14.1.2 Draft Redlined Labeling Text (USPI)



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24 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

√ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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6/20/06

Jeff Summers, Clinical Reviewer, DBOP, date

6/20/06

Joseph Gootenberg, Team Leader, DBOP, date

Patricia Keegan, Division Director, DBOP, date

ORIG
CC: Div. File/HFD-107
CC: J Summers/HFD-107
C:J:\\SUMMERS\STN 125085.74

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125085 / Supp 0074

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
Biometrics Division: Biologic Therapeutics Statistical Staff

STATISTICAL KEY WORDS:	**Log-rank statistic; Cox's regression model**
sBLA NUMBER:	**BLA125085/74** 6-1-06
DRUG NAME:	**Avastin ™ (Bevacizumab)**
INDICATION:	_____ b(4)
SPONSOR:	**Genentech, Inc.**
STATISTICAL REVIEWER:	**Yuan-Li Shen, Ph.D.**
STATISTICAL TEAM LEADER:	**Mark Rothmann, Ph.D.**
BTSS DIRECTOR:	**Aloka Chakravarty, Ph.D.**
CLINICAL REVIEWERS:	**Jeff Summers, M.D.**
CLINICAL TEAM LEADER:	**Joe Gootenberg, M.D.**
PROJECT MANAGER:	**Sharon Sickafuse, M.S.**

Distribution: BLA 125084/74
J. Summers
J. Gootenberg
P. Keegan
S. Sickafuse
Y. Shen
M. Rothmann
A. Chakravarty
R. O'Neill
L. Patrician

File Directory: C:/BLA_2006/Bevacizumab/Bevacizumab_colorectal CA_statreview_2006.doc

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STATISTICAL REVIEW AND EVALUATION

1 Executive Summary of Statistical Findings

The sponsor, Genentech, Inc., is seeking supplemental labeling claims of Avastin® in combination with 5-FU/LV and oxaliplatin (FOLFOX4) for treatment of metastatic carcinoma of the colon or rectum in patients previously treated with irinotecan and 5-FU/LV and oxaliplatin. 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

The results of the Phase III (study E3200), open-label, randomized, controlled study demonstrated a statistically significant improvement of overall survival in the FOLFOX4+ bevacizumab arm as compared with FOLFOX4 alone arm and also as compared with bevacizumab alone arm. The trend of beneficial treatment effect in FOLFOX4+bevacizumab arm on overall survival was consistently shown in various subgroups, such as race, gender and ECOG performance status, etc. However, the comparison of bevacizumab alone arm versus FOLFOX4 arm did not show statistical significant difference.

Deficiencies in imaging data and prior cancer treatment data collection were noted. Due to these deficiencies, the progression free survival endpoint can not be confirmed. The intended patient population:

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can not be verified.

1.2 Brief Overview of Clinical Studies

The sponsor submitted a Phase III study results (study E3200) for patients with advanced colorectal cancer who have failed therapy with irinotecan and 5-flurouracil when treated with oxaliplatin, 5-fluorouracil and leucovorin with or without bevacizumab or bevacizumab alone. The study was submitted to support the following proposed claim :

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Study ECOG E3200

This study was a multicenter, open-label, Phase III, randomized and control trial to evaluate the efficacy of bevacizumab + oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX4) versus FOLFOX4 alone versus bevacizumab alone in previously treated patients with advanced colorectal cancer.

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 for trial monitoring, data flow, and adverse event monitoring.

Eligible patients had measurable, histologically confirmed, metastatic colorectal cancer that had been previously treated with irinotecan and 5-FU or in patients who relapsed within 6 months after adjuvant therapy . Patients were randomized to the following three arms in a 1:1:1 ratio to FOLFOX4 + bevacizumab, FOLFOX4 alone and bevacizumab alone arm, respectively. A stratified randomization scheme was used based on ECOG performance status (0 vs. $\geq$ 1) and prior radiation therapy (yes, vs. no).

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 analysis of overall survival consists of each pair-wise comparison at the two-sided 0.0167 significance level.

1.3 Statistical Issues and Findings

The primary efficacy result based on overall survival from study E3200 is significant in favor of FOLFOX4+bevacizumab arm. The median survival times are 10.8 months (95% C.I.=[10.1,11.9]) and 13.0 months (95% C.I.=[12.1,14.0]) for FOLFOX4 alone arm and FOLFOX4+bevacizumab arm, respectively. However, the comparison of bevacizumab alone arm versus FOLFOX4 arm did not show a statistical significant difference . The bevacizumab alone arm shows significantly higher risk in overall survival as compared with FOLFOX4+bevacizumab arm (hazard ratio of FOLFOX4 alone arm versus FOLFOX4+bevacizumab is 1.33 with 95% C.I.=[1.11,1.59]).

There are a few statistical issues related to the analyses:

- The sponsor's intended claimed patient population _____ b(4)
  _____ can not be confirmed since data collection of prior cancer treatment is not adequate.
- The bevacizumab monotherapy arm was terminated one month prior to the end of patient enrollment. The effect of dropping an arm during the study may potentially impact the efficacy evaluation. The reviewer performed analyses based on Cox's proportional hazards model, including patients from three arms and stratified by whether patients enrolled prior or after termination of bevacizumab monotherapy arm. The results appear to agree with the sponsor's final analyses results.

whether patients enrolled prior or after termination of bevacizumab monotherapy arm. The results appear to agree with the sponsor's final analyses results.

- Due to the faster enrollment of 660 patients than anticipated (14 months instead of 22 months), ECOG increased the sample size from 660 to 880 . The rationale of modification of the sample size does not seem to be well justified. If the overall study duration was fixed as planned (31 months), even with shorter enrollment period, it is not clear why the required number of events based on a longer follow-up time can not be reached (17 months, instead of 9 months) and the sample size would need to be increased.
- Since imaging data was not collected based on standard procedure, the claim for disease progression or objective response can not be confirmed.

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

The sponsor submitted the results from a multicenter, randomized, open-label, Phase III trial of bevacizumab + oxaliplatin fluorouracil and leucovorin (FOLFOX4) versus FOLFOX4 alone versus bevacizumab alone in previously treated patients with advanced colorectal cancer. Patients with confirmed, advanced or metastatic colorectal cancer that had been previously treated with a 5-FU regimen and an irinotecan-based regimen were enrolled. 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 original proposed comparisons are between any two arms : FOLFOX4+bevacizumab versus FOLFOX4 alone arm, FOLFOX4+bevacizumab versus bevacizumab alone arm and FOLFOX4 alone arm versus bevacizumab alone arm 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 efficacy data analysis are summarized below:

- The sponsor's intended claimed patient population "_____ b(4)
_____ The data collection for the prior cancer treatment was not adequate.
- The bevacizumab monotherapy arm was terminated one month prior to the end of patient enrollment. The effect of dropping an arm during the study may potentially impact the efficacy evaluation. The reviewer performed analyses based on Cox's proportional hazards model, including patients from three arms and stratified by whether patients enrolled prior or after termination of bevacizumab monotherapy arm. The results appear to agree with the sponsor's final analyses results.
- Due to the faster enrollment of 660 patients (approximately 14 months instead of 22 months) and concern of losing power based on the planned follow-up time (9 months), ECOG increased the sample size from 660 to 880 . If the overall study duration was fixed as planned (31 months), even with shorter enrollment period, it is not clear why the required number of events based on a longer follow-up time can not be reached (17 months, instead of 9 months) and the sample size would need to be increased. The rationale of modification of the sample size does not seem to be well justified.
- Since imaging data was not collected based on standard procedure, the claim for disease progression or objective response can not be confirmed.

2.2 Data Sources

Data used for review is from the electronic submission received on 12/15/05. The network path is \\Cbsap58\m\EDR Submissions\2005 BLA\DCC60002256\blamain".

3 Statistical Evaluation

The efficacy analysis results will be presented in this section for protocols E3200.

3.1 Evaluation of Efficacy

3.1.1 Study E3200

This subsection will present the efficacy evaluation for study E3200. This will include the background information, efficacy endpoints, sample size determination, the efficacy methods used, and the statistical findings.

3.1.1.1 Introduction

This study was a multicenter, Phase III, randomized, open-label, controlled study to evaluate the efficacy of bevacizumab + oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX4) versus FOLFOX4 versus bevacizumab alone in previously treated patients

with advanced colorectal cancer. The study was designed to have three pairwise comparisons of overall survival, each at a 2-sided 0.0167 significance level.

This trial was 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 for trial monitoring, data flow, and adverse event monitoring. Genentech is not involved in the conduct of the trial.

Eligible patients had measurable, histologically confirmed, advanced or metastatic colorectal cancer that had been previously treated with a 5-FU regimen and an irinotecan-based regimen. Patients were randomized to the following three arms in a 1:1:1 ratio:

- Arm A: FOLFOX4 + bevacizumab,
- Arm B: FOLFOX4 alone,
- Arm C: bevacizumab alone.

A summary of the three regimen is provided in the following table by the sponsor:

Table 1 Sponsor's Summary of Treatment Regimens for Study E3200

Arm/Agent	Dose	Route	Treatment Administration
Arm A			
Bevacizumab	10 mg/kg	IV infusion over 90 min [a]	Day 1
Oxaliplatin	85 mg/m^2	IV in 250–500 mL of D5W over 120 min	Day 1
Leucovorin	200 mg/m^2	IV infusion over 120 min	Days 1 and 2
5-FU	400 mg/m^2 600 mg/m^2	IV bolus followed by IV infusion over 22 hr	Days 1 and 2
Arm B			
Oxaliplatin	85 mg/m^2	IV in 250–500 mL of D5W over 120 min	Day 1
Leucovorin	200 mg/m^2	IV infusion over 120 min	Days 1 and 2
5-FU	400 mg/m^2 600 mg/m^2	IV bolus followed by IV infusion over 22 hr	Days 1 and 2
Arm C			
Bevacizumab	10 mg/kg	IV infusion over 90 min a	Day 1

5-FU = 5-fluorouracil; IV = intravenous. Note: Dose calculations are based on actual body weight at the beginning of each cycle. Drugs are administered in the order listed in the table.

[a] 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.

Stratified randomization was performed based on the following stratification factors:

- ECOG performance status (0 vs. $\geq$ 1)
- Prior radiation therapy (yes, vs. no).

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

- To evaluate response, time to progression, and overall survival of patients with advanced colorectal cancer who have failed therapy with irinotecan and 5-fluorouracil when treated with oxaliplatin, 5-fluorouracil and leucovorin with or without bevacizumab or bevacizumab alone.
- To define the toxicity of these regimens.

For regulatory submission purposes, the sponsor specified the following primary objectives on the April 13, 2004 statistical analysis plan (SAP):

- To evaluate the efficacy of bevacizumab when combined with FOLFOX4 versus FOLFOX4 alone in patients with advanced colorectal cancer who have failed therapy with irinotecan and 5-fluorouracil, as measured by duration of survival.
- To evaluate the safety of bevacizumab when combined with FOLFOX4 versus FOLFOX4 alone in patients with advanced colorectal cancer who have failed therapy with irinotecan and 5-fluorouracil.

The secondary objective as stated in the SAP was

- To evaluate the efficacy of bevacizumab when combined with FOLFOX4 versus FOLFOX4 alone in patients with advanced colorectal cancer who have failed therapy with irinotecan, 5-fluorouracil and leucovorin, as measured by progression-free survival, objective response, and duration of objective response.

Reviewer's comment : Based on original plan, pair-wise comparison between FOLFOX4 alone arm, FOLFOX4+bevacizumab arm and bevacizumab alone arm are listed as the primary comparisons.

Treatment regimens were repeated every cycle (2 weeks) until disease progression, except that treatment was discontinued for patients who either achieved a partial response and underwent surgical resection of all existing disease or achieved a complete

response and completed up to two additional cycles of treatment. There was no limit of the maximum number of cycles of study treatment.

Patients who discontinued the study treatment continued to be followed for survival and tumor response until disease progression or death.

Overall tumor burden was evaluated by the investigator using the Response Evalution Criteria in Solid Tumors (RECIST) at baseline and every 8 weeks while on study treatment. Complete response (CR) and partial response (PR) were confirmed ≥ 4 weeks after the criteria for response were first met.

Patients who discontinued protocol therapy prior to progression continued to be evaluated for tumor response until disease progression, but the protocol did not specify the frequency of tumor assessments after completion of protocol therapy.

Patients who discontinued or completed study treatment followed similar tumor evaluation schedule for survival.

Toxicity forms were collected monthly during the first six cycles of treatment then every 3 months while on treatment, including data from 30 days following the last dose received.

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	Folfox4[a]	Folfox4 + Bevacizumab	Bevacizumab
E3200	11/13/01-4/28/03 (enrollement completed)	Randomized	292	293	244
		Not Treated	7 (2.4%)	6 (2.0%)	10 (4.1%)
		Safety Evaluable	285 (97.6%)	287 (98.0%)	234 (95.9%)
	Study completion occurred at Aug 1, 2005 (date of ECOG database transfer)	Treatment discontinuation	285 (97.6%)	287 (98.0%)	233 (95.5%)

[a] FOLFOX4 : oxaliplatin/5-fluorouracil/leucovorin
Note : This is based on ECOG data transfer on August 1, 2005.

At the time of the first patient enrolled (Nov. 13, 2001), the study was conducted based on the original protocol and first addendum. There were eight amendments to the protocol occurred on October 30, 2001, October 16, 2002, February 13, 2003, February

26, 2003, May 28, 2003, December 19, 2003, January 26, 2005 and April 6, 2005. Most of the amendment were either related to safety evaluation or were administrative. The amendments that may affect the efficacy evaluation include:

- October 16, 2002 :
  1. Measurable disease requirement was removed as a stratification factor.
  2. Clarified that patients on the FOLFOX4 + bevacizumab arm who required discontinuation of both 5-FU and oxaliplatin for toxicity could continue to receive bevacizumab.
  3. Clarified that patients in the FOLFOX4 arm who required discontinuation of both 5-FU and oxaliplatin for toxicity would be removed from the study.
  4. Clarified that patients in the FOLFOX4 + bevacizumab arm who required discontinuation of bevacizumab due to toxicity could continue to receive oxaliplatin and 5-FU.
  5. Clarified that patients in the bevacizumab monotherapy arm who required discontinuation of bevacizumab due to toxicity would be removed from the study.
  6. Clarified that patients who undergo surgical resection of all existing disease will be removed from the study and should have PR reported as best response to therapy.

- February 26, 2003 : The statistical consideration section was updated to account for expanded accrual. The planned enrollment was increased to 880 total patients. (Enrollment finished on April 28, 2003).

Reviewer's comment : Measurable disease was removed as a stratification factor in the second amendment (October 16, 2002). Before the second amendment, there were 169, 174 and 173 patients randomized in FOLFOX4 alone arm, FOLFOX4+bevacizumab and bevacizumab alone arm, respectively.

Prior to the first formal interim efficacy analysis, the bevacizumab alone arm was closed to further enrollment on March 11, 2003, based on a review of early results by the ECOG Data Monitoring Committee (DMC), which suggested possibly decreased overall survival for patients in the bevacizumab alone arm compared to either of the other arms.

Based on the protocol, the study was monitored by the ECOG DMC at bi-annual meetings. Per protocol, study enrollment was suspended after 50 patients enrolled per treatment arm in order to perform a preliminary toxicity review. This review occurred as planned and no changes to the study were recommended at that time. Subsequently, the study was re-opened.

In the original protocol, it stated that interim analyses for efficacy were to be conducted at 50% and 75% of the total deaths. It was observed during the November 3, 2003 DMC

(based on data cutoff date of September 8, 2003) that the study had not reached 50% of the total death required, so the first efficacy interim analysis was not performed at that time. The actual first efficacy interim analysis was performed on April 27, 2004 DMC meeting (data cutoff date of March 5, 2004; include 71% of the total planned information of 460 deaths). The DMC recommended that the protocol specified criteria for early stopping had not been met and the study was continued.

The second efficacy interim analysis was conducted on November 2, 2004 (with data cutoff date of September 7, 2004, about 6 months after the data cutoff date for the first efficacy interim analysis; include 90% of the total planned information of 460 deaths). Based on this review, the ECOG DMC determined that the pre-specified criteria met for statistical significance for the comparison of FOLFOX4+bevacizumab versus FOLFOX4.

The original statistical analysis plan dated Feb. 20, 2004 was amended on April 13, 2004 based on the agency's recommendation (after a meeting on March 23, 2004). The major changes are summarized as follows:

- The secondary endpoints and procedures for adjustment for multiplicity were clarified
- Additional information on the level of difference in censoring patterns for survival was included
- Additional details regarding the analysis of efficacy and safety data for bevacizumab monotherapy arm were added.
- The definition of disease progression was clarified to state that only radiologic evidence was used to detect tumor progression.
- An exploratory analysis plan for calculating the joint probability of the superiority of the FOLFOX4+bevacizumab arm compared with the FOLFOX4 and bevacizumab monotherapy arm was added.

Reviewer's note : The statistical analysis plan (SAP) was finalized (Feb. 20,2004), about 2 months prior to the first interim analysis (April 27, 2004). The SAP was amended about 2 weeks prior to the first interim analysis.

3.1.1.2 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 at the time of analysis were censored at the date that the patient was last known to be alive. Note that based on ECOG policy, all patients registered to an ECOG study are followed until death.

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

Overall response : Definition of overall response is based on the combination of tumor responses in target and non-target lesions, as well as the presence or absence of new lesions (as shown in the following table). Best overall response is the best response recorded from the start of study treatment to disease progression/recurrence. The definition of overall response based on the combination of tumor responses in target and non-target lesions, along with the presence or absence of new lesions at each time point is listed as follows:

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 CR or PR overall response, confirmed by repeat assessments performed by the investigator $\geq$ 4 weeks after the criteria for response are first met.

Duration of Objective Response : Defined as the duration from the time that the measurement criteria are met for a CR or PR (whichever occurred first) to the time of disease progression or death from any cause within 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.

Note : objective response (CR or PR) was confirmed by repeat assessments performed by the investigator $\geq$ 4 weeks after the criteria for response are first met. Patients who did not meet this criterion, including patients who did not have a post–baseline tumor assessment will be considered as non-responder.

Progression-Free Survival (PFS) : Defined as the duration from the time of randomization to disease progression or death from any cause within 30 days following discontinuation of study treatment. Patients without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Tumor assessments performed more than 60 days following the date of last protocol therapy or after the start of non-protocol therapy (when available) were not considered in the

analyses of PFS. The 60-day interval was based on the frequency of scheduled tumor assessments (every 8 weeks).

Patients who receive non-protocol-specified therapy prior to experiencing documented disease progression will be censored at the time of the last tumor assessment. Since patients who discontinue study treatment due to toxicity undergo disease assessments at intervals different from those mandated on study treatment, patients who discontinue study treatment prior to disease progression was censored at the time of the last tumor assessment prior to discontinuation of study treatment.

Note : 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.

3.1.1.3 Sample Size Consideration

Based on the original protocol design, a total of 660 eligible patients (~ 693 total patients by allowing 5% ineligibility) would be enrolled. This original design targeted 22 months of accrual and 9 months of follow-up. Due to a faster accrual rate than originally expected, with 9 months follow-up as originally planned, the original planned sample size (n=660) has only roughly 87% power to detect a 50% difference in median overall survival. Therefore, ECOG revised the study sample size to include 837 eligible patients (~ 880 total patients by allowing 5% ineligibility). This sample size has greater than 95% power when the hazard ratio for overall survival is 0.67 for FOLFOX4+bevacizumab versus FOLFOX4 alone (Effective in protocol amendment 4, February 26, 2003) using the log-rank test at an overall 2-sided α=0.0167 adjusted for two interim analyses. This new sample size was expected to accrual over 18 months with 13 months of follow-up. The hazard ratio corresponds to a 50% improvement in the median time to death from 7 months to 10.5 months. This sample size also had greater than 88% power when the hazard ratio for overall survival is 0.71 for FOLFOX4+vevacizumab versus FOLFOX4 alone. This corresponds to a 40% improvement of median survival time from 7 months to 9.8 months.

In the statistical analysis plan, it is noted that the full information for the primary endpoint of overall survival is not explicitly stated in the protocol. The blinded Data Monitoring Report dated March 26, 2003 states that a total of 453 deaths in the primary comparison arms (i.e. Arms A and B). However, in a more recent sponsor's correspondence with ECOG (dated February 2004), it states a total of 460 deaths in the primary comparison arms represented full information for the final analysis of duration of survival .

Based on the revised sample size, it would have a 92% power when there is a 40% improvement in median PFS from 4 months (assume 4 months median PFS in the

FOLFOX 4 arm) to 5.6 months and an 85% power when there is a 35% improvement in median PFS from 4 months to 5.4 months.

In addition, the revised sample size can provide 80% power to detect a 10% absolute difference in response rate (from 10% to 20%) using a two-sample comparison of binomials with an alpha level of 0.0167.

3.1.1.4 Efficacy Analysis Method

The primary efficacy analysis was based on a comparison of the FOLFOX4+bevacizumab arm versus FOLFOX4 arm using the log-rank test stratified by ECOG performance status and prior radiation therapy. 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.

Based on the original protocol, there were three pre-specified pairwise comparisons : FOLFOX4+bevacizumab arm versus FOLFOX4 arm, FOLFOX4+bevacizumab versus bevacizumab alone arm and FOLFOX4 versus bevacizumab alone. These three comparisons, as well as the two planned interim analyses, will be taken into account during analysis so that the overall type I error rate for the primary endpoint of overall survival will be controlled at two sided α=0.05 level. In the final statistical plan (April 13, 2004; from Genentech), it specified that the primary comparison of duration of survival between FOLFOX4+bevacizumab arm versus FOLFOX4 alone will be performed with an overall type I error rate of α=0.0167. Results are provided later in tables.

For the secondary endpoint (PFS and objective response), the comparison between FOLFOX4 arm versus FOLFOX4+bevacizumab will also be performed with an overall type I error rate of α=0.0167.

The O'Brien-Fleming group sequential boundary function was used to adjust for the sequential testing, and the alpha-spending function of Lan-DeMets was used to adjust for the boundaries if the actual interim analyses do not correspond to the projected analysis times of 50% and 75% information level with the targeted final evaluation at 460 deaths for FOLFOX4 arm and FOLFOX4+bevacizumab combined. The SAP indicates that following the actual interim analyses, the exact α level for the final analysis comparison will be computed.

The protocol also indicates that the study would be monitored by the ECOG DMC for early stopping in favor of the null hypothesis using repeated confidence interval methodology similar to that described by Jennison and Turnbull (1989). It is noted that

a "buying back" of type I error strategy was not used in this analysis. Analyses performed by the ECOG DMC concerning futility was assumed to have no effect on the type I error rate.

For the missing data, the sponsor indicated that for duration of survival, patients who are lost to follow-up will be censored on the date the patient was known to be alive. For progression-free-survival, data for patients who are lost to follow-up will be censored to the last date that the patients was known to be progression free. For patients who are randomized, not treated, and immediately lost to follow-up will be censored on the randomization date + 1 for progression-free-survival. For objective response, patients who do not have a post-baseline tumor assessment will be counted as non-responders. Results are provided later in tables.

Sensitivity analysis for overall survival was also performed per agency's request (letter dated June 5, 2003). In this analysis, patients who were lost to follow-up for survival were analyzed as events rather than as censored observation. Analyses were performed based on two definition of lost-to-follow-up : last contact date >3 and > 6 months prior to the date the final database was received by the sponsor.

Also per agency's recommendation, the SAP specified that evaluations of early discontinuations will be performed. The analyses will included a summary of reason for treatment discontinuation, the total number of cycles of study treatment provided, and the number of any other unplanned dose modifications or additions to/omissions of study treatment. Results are given in tables.

The PFS was analyzed based on the similar statistical methods used for the overall survival.

The objective response rates were compared based on Cochran-Mantel-Haenszel test stratified by ECOG performance status and prior radiation therapy. The objective response rate estimate and the 95% confidence interval were presented based on normal approximation to the binomial distribution.

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 comparison between bevacizumab alone arm versus FOLFOX4 alone arm and bevacizumab alone arm versus FOLFOX4+bevacizumab arm are considered as exploratory analyses in the analysis plan. These exploratory analyses include evaluation of duration of survival, PFS, objective response and duration of objective

response. The analysis methods used for these exploratory analyses were similar to those used for the primary analyses. These comparisons were based on full population, including those patients from the two principal arms (FOLFOX4+bevacizumab and FOLFOX4 alone arm) who were enrolled after discontinuation of the bevacizumab monotherapy arm. It is noted from the statistical analysis plan, that only patients from Arm A (or Arm B) who were concurrently randomized with Arm C patients will be included, however the full population was used for the exploratory analyses in the submission. Genentech indicates that the difference of the recruit time of full population and the concurrently enrolled patient population was only 1 months (March 11, 2003 to April 28, 2003 when the enrollment was completed), so the two populations are basically overlapped.

The effect of demographic and baseline prognostic characteristics on overall survival were examined for the principle 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, race (white, non-white), number of involved sites (1,>1), baseline CEA (carcinoembryonic antigen) value (> ULN, ≤ ULN) and baseline sum of the longest diameters of target lesions (≥ median, < median).

Subgroup analyses for overall survival and the principal arms 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, an Cox proportional hazards model including treatment and each individual variable was fitted. The initial multivariate model including the effects of treatment and all variables that were individually significant was also examined. The final multivariate model excluded variables that were not significant in the initial model.

3.1.1.5 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 (August 1 ,2005) which ECOG judged to be valid for inference for this study. [Are these dates, here and below, data cutoff dates or the dates that Genentech received the data]
- The NCI AdEERS database was provided by NCI to Genentech (August 23, 2005), which included events with onset on or before June 30, 2005

The following table summarizes patient disposition and reasons of discontinuation of study treatment. Over 95% of the patients received study treatment. Majority of patients ended protocol therapy due to disease progression (50%, 48% and 65% for FOLFOX4, FOLFOX4+bevacizumab and bevacizumab, respectively) and toxicity (24%, 23% and 12% for FOLFOX4, FOLFOX4+bevacizumab and bevacizumab,

respectively). Only 2%, 2% and 4% of the patients for FOLFOX4, FOLFOX4+bevacizumab and bevacizumab arms, respectively, were not treated.

Table 4 Sponsor's Summary of Patient Disposition and Reasons of Discontinuation of Study Therapy (Study E3200)

Reason Provided by Investigator	FOLFOX4 (n = 292)	FOLFOX4 + Bevacizumab (n = 293)	Bevacizumab (n = 244)
Treated	285 (97.6%)	287 (98.0%)	234 (95.9%)
Continuing protocol therapy	0 (0.0%)	0 (0.0%)	1 (0.4%) [b]
Protocol therapy ended	285 (97.6%)	287 (98.0%)	233 (95.5%)
Treatment completed (PR with resection or CR) [a]	3 (1.0%)	3 (1.0%)	1 (0.4%)
Disease progression/relapse during active treatment	147 (50.3%)	141 (48.1%)	159 (65.2%)
Toxicity/side effects/complications	69 (23.6%)	66 (22.5%)	28 (11.5%)
Death on study	7 (2.4%)	12 (4.1%)	6 (2.5%)
Patient withdrawal or refusal	21 (7.2%)	25 (8.5%)	5 (2.0%)
Alternative therapy	4 (1.4%)	5 (1.7%)	2 (0.8%)
Other complicating disease	3 (1.0%)	4 (1.4%)	2 (0.8%)
Other	30 (10.3%)	31 (10.6%)	29 (11.9%)
Not stated	1 (0.3%)	0 (0.0%)	1 (0.4%)
Not treated	7 (2.4%)	6 (2.0%)	10 (4.1%)
Died	0 (0.0%)	1 (0.3%)	2 (0.8%)
Ineligible	1 (0.3%)	0 (0.0%)	0 (0.0%)
Refused treatment	5 (1.7%)	2 (0.7%)	5 (2.0%)
Other	1 (0.3%)	3 (1.0%)	3 (1.2%)

[a] CR = complete response; PR = partial response ; Per protocol, treatment was considered completed for patients who either achieved a PR and underwent surgical resection of all existing disease or achieved a CR and completed up to two additional cycles of treatment.

[b] One patient is shown as continuing protocol therapy, as indicated by the lack of the therapy end date. However this patient has died, and therefore no patients remain on protocol therapy.

Note: Percentages were computed relative to the number of randomized patients.
"Reason protocol therapy ended" was not provided for 1 patient in the FOLFOX4 arm (32221) and 1 patient in the bevacizumab monotherapy arm (33002).

Among all randomized patients, only 1, 7 and 1 patients in for FOLFOX4, FOLFOX4+bevacizumab and bevacizumab arm, respectively, were ineligible. The most

common reason for ineligibility was lack of measurable disease (4 in FOLFOX4+bevacizumab and 1 in FOLFOX4 patients).

The following table summarizes protocol deviation classified as major or minor by the sponsor. There were no major protocol deviation occurred in this study. The most common minor protocol deviation was the use of non-protocol therapy prior to disease progression (14% and 13% for FOLFOX4 and FOLFOX4+bevacizumab, respectively).

Table 5 Sponsor's Summary of Protocol Deviation (Study E3200)

Population	Folfox4	Folfox4 + Bevacizumab	Bevacizumab
Any major or minor protocol deviation	42 (14.7%)	44 (15.3%)	7 (3.0%)
Any major protocol deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Incorrect treatment arm given [a]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any minor protocol deviation	42 (14.7%)	44 (15.3%)	7 (3.0%)
Treatment started before registration [b]	1 (0.4%)	1 (0.3%)	0 (0.0%)
Stratification errors [c]	0 (0.0%)	1 (0.3%)	0 (0.0%)
Non-protocol anti-tumor therapy Given prior to progression/relapse [d]	39 (13.7%)	38 (13.2%)	7 (3.0%)
Chemotherapy	30 (10.5%)	26 (9.1%)	4 (1.7%)
Chemotherapy/other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chemotherapy/surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chemotherapy/radiotherapy	1 (0.4%)	1 (0.3%)	1 (0.4%)
Hormone therapy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Immunotherapy/biologic response modifier	0 (0.0%)	0 (0.0%)	0 (0.0%)
High-dose chemotherapy/stem cell transplant	0 (0.0%)	0 (0.0%)	0 (0.0%)
Surgery	3 (1.1%)	7 (2.4%)	0 (0.0%)
Surgery/other	0 (0.0%)	1 (0.3%)	0 (0.0%)
Radiotherapy	0 (0.0%)	1 (0.3%)	2 (0.9%)
Other	5 (1.8%)	0 (0.0%)	0 (0.0%)
Other deviation [e]	2 (0.7%)	7 (2.4%)	0 (0.0%)

[a] Assessed by ECOG in 710 treated patients. Information reported on the E3200 Treatment Summary Form suggested that Patient 32225 (FOLFOX4 + bevacizumab) received only FOLFOX4 (for which a query is outstanding), and that Patient 32236 (FOLFOX4) received bevacizumab instead; this was a data entry error per ECOG.

[b] Assessed in 713 treated patients.

[c]Assessed in 652 treated patients.
[d]Data were not collected for patients enrolled in the Expanded Participation Project.
[e]Assessed by ECOG in 567 treated patients.

3.1.1.5.1 Baseline Characteristics

The following table summarizes the disease characteristics including those factors used for stratification in the randomization. It shows that about equal numbers of patients with ECOG performance status of 0 and ≥ 1. Only a quarter of these patients received prior radiotherapy. The CEA (carcinoembryonic antigen) values in more than 89% patients were greater than upper limit of normal.

Table 6 Sponsor's Summary of Disease Characteristics including those used for Stratification of Subjects (Study E3200)

	FOLFOX4 (n = 292)	FOLFOX4 + Bevacizumab (n = 293)	Bevacizumab (n = 244)
ECOG performance status (baseline)			
n	291	293	244
0	148 (50.9%)	141 (48.1%)	118 (48.4%)
1	126 (43.3%)	138 (47.1%)	107 (43.9%)
2	17 (5.8%)	14 (4.8%)	19 (7.8%)
ECOG performance status category (baseline)			
n	291	293	244
0	148 (50.9%)	141 (48.1%)	118 (48.4%)
≥ 1	143 (49.1%)	152 (51.9%)	126 (51.6%)
Radiotherapy	73 (25.0%)	77 (26.3%)	64 (26.2%)
CEA (ng/mL)			
n	291	290	244
Mean (SD)	1018.6 (5124.3)	594.9 (3485.9)	596.1 (1510.7)
Median	56	61	70
Range	Range 0–56400	1–55770	1–12587
CEA category (ng/mL)			
n	291	286	244
≤ ULN	30 (10.3%)	26 (9.1%)	27 (11.1%)
> ULN	261 (89.7%)	260 (90.9%)	217 (88.9%)

CEA = carcinoembryonic antigen; ULN = upper limit of normal.

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 60 years old (ranged from 21 to 85 years old). About 60% of the patients were males and majority of the patients were White (87%).

Table 7 Sponsor's Summary of Demographic and Baseline Characteristics (Study E3200)

	FOLFOX4 (n = 292)	FOLFOX4 + Bevacizumab (n = 293)	Bevacizumab (n = 244)
Age (yr)			
n	292	292	244
Mean (SD)	60.3 (10.7)	61.3 (11.0)	59.4 (11.4)
Median	61	62	59
Range	25–84	21–85	23–82
Age category (yr)			
n	292	292	244
< 40	4 (1.4%)	9 (3.1%)	13 (5.3%)
40–64	182 (62.3%)	172 (58.9%)	141 (57.8%)
≥ 65	106 (36.3%)	111 (38.0%)	90 (36.9%)
Sex			
n	292	293	244
Female	115 (39.4%)	116 (39.6%)	99 (40.6%)
Male	177 (60.6%)	177 (60.4%)	145 (59.4%)
Race/ethnicity			
n	292	293	244
Black	20 (6.8%)	25 (8.5%)	21 (8.6%)
Filipino	1 (0.3%)	0 (0.0%)	0 (0.0%)
Hawaiian	1 (0.3%)	0 (0.0%)	0 (0.0%)
Hispanic	7 (2.4%)	10 (3.4%)	8 (3.3%)
Indian	1 (0.3%)	0 (0.0%)	0 (0.0%)
Native American	1 (0.3%)	0 (0.0%)	0 (0.0%)
Oriental	3 (1.0%)	1 (0.3%)	2 (0.8%)
White	257 (88.0%)	256 (87.4%)	208 (85.2%)
Other	1 (0.3%)	1 (0.3%)	1 (0.4%)
Unknown	0 (0.0%)	0 (0.0%)	4 (1.6%)

A summary of prior cancer treatment was provided. Types of prior cancer treatment was based on the on-study form. The prior treatment history based on ECOG Eligibility Check list was provided by study sites and data were available for 664 of the 829 randomized patients (80.1%). It is noted by Genentech that the number of prior cancer therapies received was not collected.

Based on data reported on the on-study form, about 80% of patients received adjuvant chemotherapy and 26% received radiotherapy. Based on the ECOG eligibility Check list, only very small percentage of patients had adjuvant 5-FU, followed by single-agent irinotecan (3.4% and 1.3% for FOLFOX4 alone and FOLFOX4+bevacizumab arms, respectively) or adjuvant 5-FU+irinotecan combination (1.7% and 0.9% for FOLFOX4 alone and FOLFOX4+bevacizumab arms, respectively).

Table 8 Sponsor's Summary of Prior Cancer Treatment (Study E3200)

	FOLFOX4 (n = 292)	FOLFOX4 + Bevacizumab (n = 293)	Bevacizumab (n = 244)
Prior cancer treatment			
n	292	293	244
Any	288 (98.6%)	289 (98.6%)	240 (98.4%)
Surgery	273 (93.5%)	266 (90.8%)	235 (96.3%)
Adjuvant chemotherapy	232 (79.5%)	230 (78.5%)	198 (81.1%)
Adjuvant immunotherapy	7 (2.4%)	1 (0.3%)	3 (1.2%)
Radiotherapy	73 (25.0%)	77 (26.3%)	64 (26.2%)
Prior treatment history for eligibility purpose			
n	235	235	194
Chemotherapy for advanced disease	223 (94.9%)	230 (97.9%)	188 (96.9%)
Adjuvant 5-FU; single-agent irinotecan	8 (3.4%)	3 (1.3%)	6 (3.1%)
Adjuvant 5-FU + irinotecan	4 (1.7%)	2 (0.9%)	0 (0.0%)

Note: Prior cancer treatment as reported on the E3200 On-Study Form; prior treatment history as provided on the ECOG Eligibility Checklist.

Reviewer's comment: The data based on ECOG Eligibility Checklist and E3200 on-study form were not integrated. Genentech's submitted eligibility data based on ECOG Eligibility Checklist in which only 664 out of 829 randomized patients had available data. Based on the ITT population, the results based on both study E3200on-study form and ECOG Eligibility Checklist, only approximately 80% of the patients received prior chemotherapy. It is noted that from ECOG Eligibility Checklist, only approximately 2.7% to 1% of patients received adjuvant 5-FU, followed by single-agent irinotecan and

0 to 1.3% of patients received adjuvant 5-FU+irinotecan based on ITT population. Genentech's intended claimed patient population "in patients previously treated with irinotecan and 5-FU for advanced disease or as adjuvant therapy in patients who then relapsed within 6 months" can not be supported by this eligibility data.

The following table summarizes the baseline tumor assessment. Number of sites involved and sites of organ involvement seem to be comparable between treatment groups, although the Bevacizumab alone arm seems to have somehow higher percentage of more than 1 site involvement. About 70% of the patients had involved more than 1 tumor site. The most frequently involved metastatic sites were liver (72%-76%) and lung (51%-60%).

Table 9 Sponsor's Summary of Baseline Tumor Assessment (Study E3200)

	FOLFOX4 (n = 292)	FOLFOX4 + Bevacizumab (n = 293)	Bevacizumab (n = 244)
Number of involved sites			
n	292	293	244
Mean (SD)	2.2 (1.1)	2.3 (1.2)	2.4 (1.1)
Median	2	2	2
Range	1–8	1–8	0–6
Number of involved sites category			
n	292	293	244
0	0 (0.0%)	0 (0.0%)	2 (0.8%) [a]
1	88 (30.1%)	87 (29.7%)	54 (22.1%)
> 1	204 (69.9%)	206 (70.3%)	188 (77.0%)
Sites of involvement			
n	292	293	242
Primary site or tumor bed	37 (12.7%)	35 (11.9%)	36 (14.9%)
Regional lymph nodes	50 (17.1%)	43 (14.7%)	44 (18.2%)
Distant lymph nodes	69 (23.6%)	62 (21.2%)	60 (24.8%)
Lung	148 (50.7%)	164 (56.0%)	146 (60.3%)
Liver	221 (75.7%)	214 (73.0%)	173 (71.5%)
Other abdominal	69 (23.6%)	70 (23.9%)	53 (21.9%)
Bone	17 (5.8%)	22 (7.5%)	19 (7.9%)
Brain	0 (0.0%)	1 (0.3%)	0 (0.0%)
Distant skin/subcutaneous	3 (1.0%)	6 (2.0%)	4 (1.7%)
Other	42 (14.4%)	44 (15.0%)	46 (19.0%)
SLD of target lesions (cm)			

n	267	267	225
Mean (SD)	11.8 (7.7)	11.1 (8.1)	12.4 (9.7)
Median	10	9	10
Range	1–37	1–49	1–60

SLD = sum of longest diameters. Note: Involved sites as reported on the E3200 On-Study Form; SLD as reported on the baseline tumor assessment when available.
[a] For 2 patients in the bevacizumab monotherapy arm, no sites of involvement are shown above because none were reported on the E3200 On-Study Form; however, the baseline tumor assessments for these patients indicated that 1 patient had liver disease (32263) and the other had a pre-sacral mass (33153).

Note: Other baseline information and study conduct summary, such as medical and surgical history (not collected), concomitant therapy (not collected), measurements of treatment compliance (study personnel administered study treatment) are not summarized .

3.1.1.5.2 Primary Efficacy Endpoint Analyses

Based on the second interim efficacy analysis (November 2, 2004 with data cutoff of September 7, 2004), the DMC determined that the primary endpoint of overall survival had crossed the O'Brien-Fleming boundary in favor of the FOLFOX4+bevacizumab arm and recommended that the results be release to the investigators for possible presentation and publication. This interim analysis included 90% of the total planned information of 460 deaths. The results were summarizes in the following table:

Table 10 ECOG's Summary of Overall Survival in the Principle Arms – November, 2004 Interim Analysis (Study E3200)

	ECOG-Evaluable Population	All Randomized Population
Patients in the analysis	579	NA
# of deaths	416	420
Information fraction [a]	90%	91%
Stratified analysis		
Hazard ratio [b]	0.74	0.74
p-value [c]	0.0024	0.0019
Boundary p-value [d]	0.0097	
Median survival (mo)		
FOLFOX4	10.7	NA
FOLFOX4 + bevacizumab	12.5	NA

NA = not available from ECOG's interim analysis (September 2004).
[a] Number of deaths observed divided by total information (460 deaths).
[b] Relative to FOLFOX4. Calculated by Genentech based on the hazard ratio relative to FOLFOX4+bevacizumab

(HR=1.35 and 1.36 for the ECOG-evaluable and all-randomized population, respectively). The strata are ECOG performance status (0, ≥ 1) and prior radiotherapy (yes, no).

[c] Provided by ECOG for the ECOG-evaluable population; Genentech calculated p-value for the all-randomized population based on the Wald test statistic provided by ECOG.

[d] The nominal significance level was calculated by Genentech based on the critical value provided by ECOG (2.5852).

The final analysis of the overall survival was performed based on the most current and complete efficacy data (received from ECOG on August 1, 2005). In the final analysis, the FOLFOX4+bevacizumab arm again show beneficial treatment effect on overall survival based on the stratified log rank test (p-value=0.0012). The median survival time was 10.8 months for FOLFOX4 arm and 13.0 months for FOLFOX4+bevacizumab arm. The hazard ratio between FOLFOX4+bevacizumab and FOLFOX4 was 0.751 with 95% C.I.=(0.63,0.89).

Table 11 Sponsor's Summary of Overall Survival – Final Analysis (Study E3200)

	FOLFOX4 (n=292)	FOLFOX4 + Bevacizumab (n = 293)	Bevacizumab (n=244)
# of Death	265	260	220
Censored observations	27 (9.2%)	33 (11.3%)	24 (9.8%)
Duration of survival [a] (mo)			
Median (95% CI)	10.8 (10.12, 11.86)	13.0 (12.09, 14.03)	10.2 (8.44,12.06)
Range	0.0–40.0 +	0.3–39.1 +	0.0 +–40.0 +
Stratified analysis (relative to FOLFOX4)			
Hazard ratio [b] (95% CI)	NA	0.751 (0.632, 0.893)	1.028 (0.858,1.232)
p-value (log-rank)	NA	0.0012	0.7631
Stratified analysis (relative to FOLFOX4 +bevacizumab)			
Hazard ratio [b] (95% CI)	NA	NA	1.327 (1.107,1.5951)
p-value (log-rank)	NA	NA	0.0021

CI = confidence interval; NA = not applicable; + indicates a censored value.

[a] Summary statistics are from Kaplan-Meier analysis; 95% CI was computed using the method of Brookmeyer and Crowley.

[b] Estimated by Cox regression. The strata are ECOG performance status (0, ≥1) and prior radiotherapy (yes, no).

Reviewer's Comments:

1. *Genentech performed sensitivity analysis by treating lost to follow-up for survival as events rather than as censored observation. Results based on both definitions of lost to follow-up (last contact date > 3 months and > 6 months prior to the date of the final database) showed improvement of overall survival in the FOLFOX4+bevacizumab arm (stratified log rank test p-value=0.0004).*

2. *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 results show that the censoring distributions are comparable between treatment groups (p-value=0.87).*

3. *Genentech performed analysis of the bevacizumab alone arm versus each of the FOLFOX4 alone arm and FOLFOX4+bevacizumab arm. The results show that the bevacizumab alone arm had significantly higher risk in overall survival as compared with FOLFOX4+bevacizumab arm (hazard ratio=1.327 based on Cox's model; p-value=0.0021 based on stratified log-rank test). The bevacizumab alone arm also shows higher risk in overall survival as compared to FOLFOX4 alone arm (hazard ratio=1.028 based on Cox's model, shown in Table 11), although it does not reach nominal statistical significance(p-value=0.7631 based on stratified log-rank test) .*

4. *It is noted that 47 out of 292 FOLFOX4 arm and 42 out of 293 FOLFOX4+bevacizumab arm were enrolled after bevacizumab alone arm was terminated (March 11, 2003). If these patients were excluded from the analysis of overall survival, the FOLFOX4+bevacizumab still shows beneficial effect in overall survival. However, Bevacizumab monotherapy group seems to have increased risk as compared with FOLFOX4+bevacizumab arm. The results are shown in the table below :*

Table 12 Reviewer's Summary of Overall Survival – Based on population enrolled prior to Termination of Bevacizumab monotherapy (March 11, 2003) (Study E3200)

	FOLFOX4 N=292	FOLFOX4 + Bevacizumab N=293	Bevacizumab N=244
#patients enrolled prior to 3/1//03	(n=245)	(n = 251)	(n=244)
# of Death	230	226	220
Censored observations	15 (6.1%)	25 (10.0%)	24 (9.8%)
Duration of survival [a] (mo)			
Median (95% CI)	10.8 (10.1, 11.9)	12.8 (12.0, 13.4)	10.2 (8.4,12.1)
Range	0.03+–40.0 +	0.4–39.1 +	0.0 +–40.0 +
Stratified analysis (relative to FOLFOX4)			
Hazard ratio [b] (95% CI)	NA	0.73 (0.61,0.88)	0.98 (0.82,1.19)
p-value (stratified log-rank)		0.0009	0.8577
Stratified analysis (relative to FOLFOX4+Bevacizumab)			

Hazard ratio [b] (95% CI)	1.30 (1.08,1.57)
p-value (stratified log-rank)	0.0057

[a] Summary statistics are from Kaplan-Meier analysis.
[b] Hazard ratio estimated by Cox regression. The strata are ECOG performance status (0, ≥1) and prior radiotherapy (yes, no).
NA: Not Applicable; + Indicate a censored value.

5. *A Cox's proportional hazards model was fitted based on all randomized patients stratified by whether patients were enrolled prior to termination of bevacizumab or not. The pairwise comparison results based on the Cox's model further confirm the previous results.*

   Note: The pairwise comparisons were based on Wald statistic from the Cox's proportional hazards model using FOLFOX4 arm as the reference group in the model. The hazard ratio estimate and the confidence interval of the hazard ratio estimate between bevacizumab monotherapy versus FOLFOX4+bevacizumab were calculated based on exponentiation of the linear combination of the parameter estimates from the model.

Table 13 Reviewer's Summary of Overall Survival – Based on All Randomized Population, Stratified by Bevacizumab Monotherapy Termination Date (before and after March 11, 2003) Cox's Proportional Hazards Model (Study E3200)

	FOLFOX4 N=292	FOLFOX4 + Bevacizumab N=293	Bevacizumab N=244
Stratified analysis (relative to FOLFOX4)			
Hazard ratio [a] (95% CI)	NA	0.76 (0.64,0.90)	0.96 (0.80,1.15)
p-value [b](Wald statistic)		0.0018	0.6293
Stratified analysis (relative to FOLFOX4+Bevacizumab)			
Hazard ratio [a] (95% CI)			1.26 (1.05,1.51)
p-value [b] (Wald statistic)			0.0141

[b]Hazard ratio estimates and the 95% C.I. were from the stratified Cox's proportional hazards model stratified by bevacizumab monotherapy termination date.
[b]P-value based on Wald statistic from same stratified Cox's proportional hazards model.

6. *Genentech identified 29 patients on the FOLFOX4+beacizumab arm as having received some component of FOLFOX4 for greater than 2 days after the last dose of bevacizumab. When this reviewer censored the patients who had bevacizumab discontinuation and who had taken less than 50% of FOLFOX4 total dose prior to bevacizumab discontinuation total, the result for the overall survival was still in favor of the FOLFOX4+bevacizumab (HR=0.75 with 95% C.I.=[0.63,0.90]).*

7. *Genentech also performed Cox's proportional hazards model to evaluate treatment effect (FOLFOX4+bevacizumab v.s. FOLFOX4 alone arm) after adjusting for important prognostic factors (see subgroup analysis in section 16.1.9 Documentation of Statistical Methods). Several important prognostic factors for overall survival were identified : ECOG performance status at study entry (0,≥1), prior radiation therapy (yes, no), race (white, non-white), number of involved sites (1,>1), baseline CEA (carcinoembryonic antigen) value (> ULN, ≤ ULN) and baseline sum of the longest diameters of target lesions (≥ median, < median). After adjusting for these prognostic factors, the treatment effect remains statistically significant in favor of the FOLFOX4+bevacizumab arm.*

3.1.1.5.3 Secondary Efficacy Endpoint Analyses

The progression-free survival (PFS) is summarized in the following table. The results showed that FOLFOX4+bevacizumab had longer median progression-free survival (7.5 months) as compared with that of the FOLFOX4 alone arm (4.5 months) with p value of <0.0001 from the stratified log rank test. The results also showed that over 90% of the PFS events were attributed to disease progression.

Table 14 Sponsor's Summary of Progression-Free Survival in the Principle Arms (Study E3200)

	FOLFOX4 (n = 292)	FOLFOX4 + Bevacizumab (n = 293)
Patients with an event [a]	179	177
Disease progression	169	160
Death [b]	10	17
Censored observations	113 (38.7%)	116 (39.6%)
Progression-free survival [c] (mo)		
Median (95% CI)	4.5 (4.07, 5.26)	7.5 (6.71, 8.18)
25%–75% percentile	2.7–7.6	4.2–10.0
Range	0.0–19.6	0.0 +–20.2
Stratified analysis		
Hazard ratio [d] (95% CI)	NA	0.518 (0.416, 0.646)
p-value (log-rank)	NA	< 0.0001

+ indicates a censored value.
[a] The earliest contributing event is shown.
[b] Deaths from any cause occurred within 30 days following discontinuation of protocol therapy.
[c] Summary statistics are from Kaplan-Meier analysis; 95% CI was computed using the method of Brookmeyer and Crowley.
[d] Relative to FOLFOX4. Estimated by Cox regression. The strata are ECOG performance status (0, ≥1) and prior radiotherapy (yes, no).

Reviewer's Comments:

1. *This reviewer performed stratified log rank test to evaluate treatment difference based on the progression free survival data with the censoring and event indicator switched. The results show that the a somewhat longer time to censoring in the FOLFOX4+bevacizumab arm (p-value=0.0458 based on stratified log rank test; the median time to censoring were 6.4 [95% C.I.=6.0,8.7] and 8.7[95% C.I.=7.9,11.4] for FOLFOX4 and FOLFOX4+bevacizumab arm, respectively).*

   It is noted that protocol specified tumor measurement would be performed every 8 weeks while on treatment, but did not specify tumor measurement frequency after the end of therapy. Patients were censored for PFS at the last tumor assessment before the start of non-protocol therapy and within 60 days following the end of protocol therapy. These factors may have impact on the difference in the censoring distribution.
2. *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. Further evaluation on this endpoint will not be performed.*

   Note : based on March 26, 2006 letter from Genentech, it indicates that the ECOG International Non-adjuvant Solid Tumor Coding Form [RECIST] captured the ECOG review of overall response as assessed by the investigator. The by-visit investigator tumor measurements were captured in the ECOG Follow-Up Disease Evaluation Form (FUDEF). It appears that the by-visit tumor evaluation was primary based on each investigator's judgment.

The following table shows the objective response summarized by Genentech. The FOLFOX4+bevacizumab arm appears to have higher objective response rate as compared with the FOLFOX4 alone arm (22.2% and 8.6% for FOLFOX4+bevacizumab and FOLFOX4 alone arm, respectively; p-value<0.0001 based on Cochran-Mantel-Haenszel test).

Table 15 Sponsor's Summary of Objective Response (Study E3200)

	FOLFOX4 N = 292	FOLFOX4 + Bevacizumab N = 293
Objective response [a] (%)	25 (8.6%)	65 (22.2%)
95% CI [b]	(5.7%, 12.5%)	(17.6%, 27.5%)
P-value [c]	NA	< 0.0001
Rate difference [d]	NA	13.6%
95% CI [b]	NA	(7.9%, 19.4%)
Best objective response		
Complete response	2 (0.7%)	5 (1.7%)
Partial response	23 (7.9%)	60 (20.5%)

[a] Complete or partial response (RECIST).
[b] Based on normal approximation.
[c] The p-value is based on the Cochran-Mantel-Haenszel test stratified by ECOG performance status (0, ≥1) and prior radiotherapy (yes, no).
[d] Relative to FOLFOX4.

The following table shows the duration of objective response summarized by Genentech. The median duration of response based on the responders does not seem to be different between treatment groups (6.0 and 6.2 months for FOLFOX4+bevacizumab and FOLFOX4 alone arm, respectively). Since the imaging data was not adequately collected, further evaluation of the objective response and duration of objective response was not performed.

Table 16 Sponsor's Summary of Duration of Objective Response (Study E3200)

	FOLFOX4 N=292	FOLFOX4 + Bevacizumab N=293
Patients with an objective response	25	65
Patients with an event [a]	13	33
Censored observations	12 (48.0%)	32 (49.2%)
Duration of objective response [b] (mo)		
Median	6.0	6.2
95% CI	(4.63, 6.21)	(5.85, 7.66)
25%–75% percentile	4.5–8.3	4.6–9.5
Range	1.8 + –8.3	0.0 + –13.7

+ indicates a censored value.
[a] Disease progression or death.
[b] Summary statistics are from Kaplan-Meier analysis; 95% CI was computed using the method of Brookmeyer and Crowley.

3.1.1.6 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Genentech concluded that the addition of bevacizumab to FOLFOX4 chemotherapy in previously treated patients with advanced colorectal cancer resulted in clinical meaningful and statistically significant prolongation of survival. The survival benefit in the bevacizumab + FOLFOX4 regimen was seen in the pre-specified patient subgroups defined by age, sex, race, ECOG performance status, prior radiotherapy, number of involved sites, and baseline tumor burden. There is no significant difference in overall survival between bevacizumab monotherapy and FOLFOX4 alone arms.

This reviewer's confirmed Genentech's overall survival results that show a beneficial treatment effect in favor of bevacizumab+FOLFOX4 arm : the median survival times were 13 months and 10.8 months for bevacizumab+FOLFOX4 arm and FOLFOX4 alone arm, respectively. Also, this reviewer did not find significant treatment difference in overall survival between the FOLFOX4 alone and bevacizumab alone arms. However, the results show that the bevacizumab alone arm had significantly higher risk in overall survival as compared with FOLFOX4+bevacizumab arm (hazard ratio=1.327 based on Cox's model; p-value=0.0021 based on stratified log-rank test).

The sponsor also made inferences based on progression free survival and objective response rate. Since the imaging data was not collected based on standard operating procedure, the validity of the progression free survival results can not be confirmed. Therefore, further evaluation of PFS was not performed.

For sub-group analysis results, please refer to Section 4.

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 FOLFOX4+bevacizumab arm consistently showed lower risk than the FOLFOX4 alone group (hazard ratio ≤ 1) across gender.

Table 17 Reviewer's Summary of Overall Survival in the Primary Arms by Gender (Study E3200)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio	FOLFOX4		FOLFOX4+ bevacizumab	
					# of patients	Median survival time (95%C.I.)	# of patients patients	Median survival time (95%C.I.)
Overall Survival	Female	231	0.0110	0.70(0.53,0.92)	115	10.3(8.5,11.9)	116	12.5(11.4,15.9)
	Male	354	0.0210	0.77(0.61,0.96)	177	11.1(10.3,13.1)	177	13.0(12.1,14.6)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.

Note: "-" indicates that the median survival time had not reached by the cut-off date.

4.2 Race

Sub-group analyses based on race subgroup for overall survival were performed by this reviewer. The FOLFOX4+bevacizumab arm consistently showed lower risk than the FOLFOX4 alone arm (hazard ratio ≤ 1) across race subgroups.

Table 18 Reviewer's Summary of Overall Survival by Race (Study E3200)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio	FOLFOX4		FOLFOX4+ bevacizumab	
					# of patients	Median survival time (95%C.I.)	# of patients patients	Median survival time (95%C.I.)
Overall Survival	White	513	0.0020	0.75(0.62,0.90)	257	11.0(10.3,12.2)	256	13.1(12.2,15.2)
	Non-white	72	0.2160	0.74(0.46,1.19)	35	8.8(6.5,11.5)	37	11.6(9.0,14.0)

[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; $\geq$ 65 years old) for overall survival were performed by this reviewer. In general, the FOLFOX4+bevacizumab arm consistently showed lower risk than the FOLFOX4 alone arm (hazard ratio ≤ 1) across age group. However, the benefit of FOLFOX4+bevacizumab group on overall survival in older population ($\geq$ 65 years old) is less clear.

Table 19 Reviewer's Summary of Overall Survival by Age Subgroup (Study E3200)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio	FOLFOX4		FOLFOX4+ bevacizumab	
					# of patients	Median survival time (95%C.I.)	# of patients patients	Median survival time (95%C.I.)
Overall Survival	<65	367	0.0040	0.72(0.58,0.90)	186	11.7(10.3,12.8)	181	13.1(12.0,15.4)
	≥65	217	0.1150	0.80(0.60,1.06)	106	10.1(8.1,11.0)	111	12.5(11.3,14.6)

[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. FOLFOX4+bevacizumab arm had consistently longer median survival time across various subgroups.

Table 20 Reviewer's Summary of Overall Survival by Baseline Prognostic Factors (Study E3200)

Endpoint	Level	# of Patient s	P-value[a]	Hazard Ratio	FOLFOX4		FOLFOX4+ bevacizumab	
					# of patients time	Median survival (95%C.I.)	# of patients patients	Median survival time (95%C.I.)
ECOG performance status	0	289	0.0200	0.74(0.58,0.95)	148	12.4(11.0,14.1)	141	16.6(14.6,18.4)
	≥1	295	0.0210	0.75(0.59,0.96)	143	9.3(8.4,10.7)	152	10.8(10.0,12.0)
CEA	≤ ULN[b]	56	0.7390	1.11(0.6, 2.03)	30	13.1(8.8,25.7)	26	16.8(11.6,19.9)
	> ULN	521	<0.001	0.72(0.60,0.86)	261	10.6(9.9,11.7)	260	12.9(12.0,13.7)
SLD[c] of target lesions (cm)	< median (9.7)	266	0.2390	0.85(0.66,1.11)	126	13.9(11.0,16.7)	140	14.5(12.5,18.0)
	≥ median	268	<0.001	0.58(0.45,0.74)	141	9.0(7.7,10.4)	127	12.1(10.4,13.4)
# of involved disease sites	1	175	0.0010	0.56(0.40,0.78)	88	11.2(9.0,13.7)	87	18.4(15.5,22.4)
	>1	410	0.1120	0.85(0.69,1.04)	204	10.5(9.9,11.7)	206	12.0(11.3,12.9)
Prior radiation therapy	NO	435	<0.001	0.70(0.57,0.85)	219	10.5(9.5,11.5)	216	13.1(12.0,14.6)
	YES	150	0.7180	0.94(0.67,1.32)	73	12.0(10.3,13.9)	77	12.5(10.5,14.8)

[a]P-value based on Wald statistic from unstratified Cox's proportional hazards model.
[b] ULN : upper limit of normal.
[c] SLD: Sum of longest diameters.

Reviewer's comment:

1. *While treatment effect seems to be different in several subgroups (e.g. CEA ≤ ULN v.s. > ULN; SLD of target lesions <median v.s. ≥median and prior radiation therapy: Yes v.s. no) based on hazard ratio estimates from the Cox's proportional hazards model, the interpretation should be taken with caution since the number of events for the subgroup is small.*
2. *Advanced disease status at registration and prior adjuvant chemotherapy (yes, no) were specified in the SAP, but were not included in the sponsor's clinical report. Due to incomplete prior cancer treatment data collection, the subgroup analysis based on prior adjuvant chemotherapy may not be meaningful.*

5 Summary and Conclusions

The sponsor submitted study E3200, a Phase III randomized, open-label, randomized, active-controlled clinical study, to support bevacizumab in combination with FOLFOX4 for the treatment of advanced colorectal cancer in previously treated patients.

In study E3200, patients were randomized to FOLFOX4 (Oxaliplatin, leucovorin and 5-FU), FOLFOX4+bevacizumab or bevacizumab monotherapy. The randomization was stratified by ECOG performance status (0 vs. ≥ 1) and prior radiation therapy (yes vs. no). Bevacizumab was administered at a dose of 10 mg/kg every two weeks for patients in the bevacizumab containing arms and prior to the FOLFOX4 arm in the FOLFOX4+bevacizumab arm on day 1. In this study, patients were treated until disease progression. Patients could continue on bevacizumab monotherapy after early discontinuation of FOLFOX4.

A total of 829 patients were enrolled into the study. Prior to March 11, 2003, there were 245, 251 and 244 patients randomized to the FOLFOX4 alone arm, FOLFOX4+bevacizumab arm, and bevacizumab alone arm, respectively. After March 11, 2003, there were 47 and 42 patients randomizedto the FOLFOX4 alone arm and the FOLFOX4+bevacizumab arm. There were 98%, 98% and 96% of the patients (in FOLFOX alone, FOLFOX4+bevacizumab and bevacizumab arms, respectively) took at least one study medication.

In study E3200, the primary efficacy endpoint was overall survival. The primary comparisons specified in the original plan were all pairwise comparisons tested at 2-sided α=0.0167 level based on the stratified logrank test. The progression free survival was designated as the important secondary efficacy endpoint. However, since the sponsor can not provide adequate imaging data to support evaluation of this endpoint, the results can not be confirmed.

A summary of the primary efficacy endpoint of study E3200 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 21 Summary of Primary and Key Secondary Efficacy Endpoint – (Study E3200)

Endpoint		FOLFOX4 (n=292)	FOLFOX4 + Bevacizumab (n = 293)	Bevacizumab (n=244)
Overall Survival	# of Death	265	260	220
	Duration of survival [a] (mo)			
	Median	10.8	13.0	10.2
	(95% CI)	(10.12, 11.86)	(12.09, 14.03)	(8.44,12.06)
	Range	0.0–40.0 +	0.3–39.1 +	0.0 +–40.0 +
	Stratified analysis (relative to FOLFOX4)			
	Hazard ratio [b]	NA	0.751	1.028
	(95% CI)		(0.632, 0.893)	(0.858,1.232)
	p-value (log-rank)	NA	0.0012	0.7631
	Stratified analysis (relative to FOLFOX4 +bevacizumab)			
	Hazard ratio [b]	NA	NA	1.327
	(95% CI)			(1.107,1.5951)
	p-value (log-rank)	NA	NA	0.0021

CI = confidence interval; NA = not applicable; + indicates a censored value.

[a] Summary statistics are from Kaplan-Meier analysis; 95% CI was computed using the method of Brookmeyer and Crowley.

[b] Estimated by Cox regression. The strata are ECOG performance status (0, ≥1) and prior radiotherapy (yes, no).

5.1 Statistical Issues and Collective Evidence

The results show a beneficial treatment effect in favor of FOLFOX4+bevacizumab arm. The median survival times were 13 months and 10.8 months for bevacizumab+FOLFOX4 arm and FOLFOX4 alone arm, respectively. The beneficial treatment effect of the FOLFOX4+bevacizumab arm (vs. FOLFOX4 alone arm) is consistently demonstrated in various subgroups : ECOG performance status, gender and rate. The consistent beneficial treatment effect is less clear in some subgroups (age,

CEA status, # of involved sites, etc), however, the results appear to show positive trend in favor of the combination arm.

The results did not show statistically significant treatment difference in overall survival between the FOLFOX4 alone and bevacizumab alone arms. In addition, the results show that the bevacizumab alone arm had significantly higher risk in overall survival as compared with FOLFOX4+bevacizumab arm (hazard ratio=1.327 based on Cox's model; p-value=0.0021 based on stratified log-rank test).

The major statistical issues were summarized as follows:

- The sponsor's intended claimed patient population "in patients previously treated with irinotecan and 5-FU for advanced disease or in patients who relapsed within 6 months after adjuvant therapy " can not be confirmed since data collection of prior cancer treatment is not adequate.
- The Bevacizumab monotherapy arm was terminated one month prior to the end of patient enrollment. The effect of dropping an arm during the study did not seem to impact the efficacy evaluation. The reviewer performed analyses based on Cox's proportional hazards model, including patients from three arms and stratified by whether patients enrolled prior or after termination of Bevacizumab monotherapy arm. The results appear to agree with the sponsor's final analyses results.
- Due to the faster enrollment (14 months instead of 22 months), ECOG increased the sample size from 660 to 880 . The rationale of modification of the sample size does not seem to be well justified. If the overall study duration was fixed as planned (31 months), even with shorter enrollment period, it is not clear why the required number of events based on a longer follow-up time can not be reached (17 months, instead of 9 months) and the sample size would need to be increased.
- Since imaging data was not collected based on standard procedure, the claim for disease progression or objective response can not be confirmed.

5.2 Conclusions and Recommendations

Based on study E3200, the results demonstrate beneficial treatment effect of FOLFOX4+bevacizumab arm on overall survival. The trend of beneficial treatment effect in FOLFOX4+bevacizumab arm on overall survival was mostly consistent across various subgroups, such as race, gender and ECOG performance status, etc.. The trend is not clear in subgroups of CEA, prior radiotherapy, etc. It is noted that interpretation of the results for subgroups should be taken with caution.

There were no significant treatment difference found between FOLFOX4 monotherapy and bevacizumab monotherapy. The effect of bevacizumab monotherapy arm shows a significantly higher risk on overall survival as compared with the FOLFOX4+bevacizumab arm.

6 SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer: **Date:** June 1, 2006

Dr. Yuan-Li Shen
Mathematical Statistician

Concurrence:

Dr. Mark Rothmann
Statistical Team Leader

Dr. Aloka Chakravarty
Director

CC:
HFD-107/ Ms. Sickafuse
HFD-107/ Dr. Summers
HFD-107/ Dr. Gootenberg
HFD-107/Dr. Keegan
HFD-711/ Dr. Rothmann
HFD-711/ Dr. Shen
HFD-711/ Dr. Chakravarty
HFD-700/Dr. O'Neill
HFD-700/Ms. Patrician

This review consists of 37 pages (32 pages of text)
C:\BLA_2006\Bevacizumab\colorectal CA_statreview 2006.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA 125085 / Supp 0074

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : STN 125085/74 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A

FDA Received Date: 12-19-05 **Action Date:** 6-20-06

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 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: Second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy

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**

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

DATE: June 20, 2006 SKS

FROM: Sharon Sickafuse, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products

TO: STN 125085/74

SUBJECT: SBA Equivalent for

- Product: Bevacizumab
- Manufacturer: Genentech, Incorporated
- License Number: 1048

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.

How Supplied
Avastin is supplied as a single-use, 4-mL vial containing 100 mg of Bevacizumab or as a 16-mL vial containing 400 mg of Bevacizumab sterile, preservative-free, injectable liquid.

Recommended Dosage
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 until disease progression.

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.

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

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

Basis for Approval

The following reviews, filed in the FDA correspondence section of the license file for STN 125085/74, comprise the SBA equivalent for this supplement:

Discipline	Reviewer Name	Date
Clinical (Safety and Efficacy)	Jeff Summers, M.D.	6-20-06
Statistical	Yuan-Li Shen, Ph.D.	6-1-06
Bioresearch Monitoring (DSI)	Lauren Iacono-Conner	5-3-06
Labeling (DDMAC)	Carole Broadnax	5-9-06, 6-1-06

68 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__√__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

LICENSING ACTION RECOMMENDATION

Applicant: Genentech, Incorporated STN: 125085/74

Product:

Bevacizumab

Indication / manufacturer's change:

Use as an adjunct to chemotherapy for the second-line treatment of patients with metastatic colorectal cancer.

■ 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 6-19-06 ☐ 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: D S Summers Date: 20-Jun-06

Product Office's Responsible Division Director(s)*:

_____ Date: _____

_____ Date: _____

DMPQ Division Director* : _____ Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

■ Compliance status checked ■ Acceptable ☐ Hold Date: 6-6-06

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) SharonSickafuse Date: 6-20-06

Responsible Division Director Patricia Keegan Date: 6-20-2006
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

ACTION PACKAGE CHECKLIST

Application Information			
BLA # 125085/74 NDA #	BLA STN# 125085/74 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: 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.)	505(b)(2) NDAs only: 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)	June 20, 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 ☐ 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?	X 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.*	X 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)*	6-18-06
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	6-20-06
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)	Final draft PI 6-19-06
• 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 5-9-06, 6-1-06 ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting/ADRA) *(indicate date of each review)*	1-31-06
❖ 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	X None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters, emails, faxes, telecons)	Approval letter 6-20-06 Revised PI email 6-16-06 D & A email 6-14-06 Revised AE section of PI email 6-13-06 Revised PI email 6-8-06 IR email 4-24-06 IR email 3-24-06 IR email 3-17-06 IR email 3-10-06 IR email 2-8-06 IR email 2-3-06 Filing & DI letter 2-17-06 STN assignment letter 1-20-06
❖ Internal memoranda, telecons, email, etc.	Midcycle meeting 4-4-06 Committee Assignment 1-12-06 Memo of priority review 1-12-06
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	3-10-05
• EOP2 meeting *(indicate date)*	
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert or minutes, if available	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	
❖ 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)*	6-14-06
• ☐ 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 ☐ Requested

❖ 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 5-11-05 X Accepted 6-6-06 ☐ 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)*	6-20-06
❖ 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)*	
❖ Microbiology (efficacy) review(s) *(indicate date of each review)*	X Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another 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)	
• Clinical studies *(include copies of DSI letters to investigators)*	5-3-06
• Bioequivalence studies *(include copies of DSI letters to investigators)*	
❖ Statistical review(s) *(indicate date of each review)*	☐ None 6-1-06
Clinical Pharmacology review(s) *(indicate date for each review)*	X None

Sickafuse, Sharon

om: Sickafuse, Sharon
nt: Friday, June 16, 2006 5:33 PM
o: 'Lisa Schain'
Subject: Bev PI - FDA's latest

Attachments: Avastin_PI_red-lined_for_FDA 061506 rev js and pk(2).doc

Avastin_PI_red-line
d_for_FDA 0...

17 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__√__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Sickafuse, Sharon

n: Summers, Jeff
Sent: Wednesday, June 14, 2006 3:41 PM
To: 'Lisa Schain'
Cc: Sickafuse, Sharon
Subject: D and A

.isa,
he following language for the Dose and Administration section would be acceptable to the DBOP and the OODP:

vastin, used in conjunction with intravenous 5-FU-based chemotherapy, is administered as an intravenous infusion every 14 days ntil disease progression.

- 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.

lope this helps.

eff

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
5600 Fishers Lane, Rockville, MD 20857
Telephone (301) 827-0850
Facsimile (301) 827-0852

Date: June 14, 2006

From: Michelle Frazier-Jessen, Ph.D., Biologist
Division of Monoclonal Antibodies, OBP/OPS/CDER/FDA

Through: Kathleen A. Clouse, Ph.D. Acting Director, DMA 6/14/06
OBP/OPS/CDER/FDA
Patrick Swann, Ph.D., Deputy Director, DMA 6/14/06
OBP/OPS/CDER/FDA

Cc: Sharon Sickafuse, RPM
OND/OODP/DBOP/CDER/FDA

To: BLA 125085/74 File

Sponsor: Genentech, Inc.
License Number: 1695
Contact: Robert L. Garnick, Ph.D.
Phone: (650) 225-1202

Subject: BLA 125085/74: Categorical Exclusion for Environmental Assessment

This supplement is to expand the indication of bevacuzimab for use in a new indication for second line treatment of colorectal cancer with chemotherapy.

The sponsor has submitted a categorical exclusion under 21 CFR 25.31 (c). There is no information indicating that additional environmental information is warranted.

The claim of categorical exemption is accepted.

Sickafuse, Sharon

Sickafuse, Sharon
Sent: Tuesday, June 13, 2006 10:38 AM
To: 'Lisa Schain'
Subject: AE section of Bev PI
Attachments: Bev PI_FDA changes_AE.doc

ere you go.

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

√ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Thursday, June 08, 2006 6:06 PM
To: 'Lisa Bell'
Subject: Bevacizumab PI for 74 minus AE section

Attachments: Bev PI_FDA changes_June 8_no AE section.doc

SIN 125085/74

Here you go. The AE section will come separately.

Bev PI_FDA
ıanges_June 8_no A

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

√ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Sickafuse, Sharon

From: Hoyt, Colleen
Sent: Tuesday, June 06, 2006 12:50 PM
To: Sickafuse, Sharon
Subject: RE: request for compliance check

STN 125085/74

Yes - they have all had acceptable Team Bio inspections within the last two years.

Colleen

From: Sickafuse, Sharon
Sent: Tuesday, June 06, 2006 12:44 PM
To: Hoyt, Colleen
Subject: RE: request for compliance check

Thanks. And the other facilities are ok too?

From: Hoyt, Colleen
Sent: Tuesday, June 06, 2006 12:24 PM
To: Sickafuse, Sharon
Subject: RE: request for compliance check

Hi Sharon -

The EIR for Genentech, Porrino, Spain, has been reviewed and evaluated by the Foreign Inspection Team and deem adequate. There are no pending or ongoing investigations that would prevent approval of 125085/74 at this time.

Colleen

From: Sickafuse, Sharon
Sent: Tuesday, June 06, 2006 11:38 AM
To: Hoyt, Colleen
Subject: RE: request for compliance check

Hi Colleen, As the action due date is in 2 weeks, can you please send me an update? Thanks

---

From: Hoyt, Colleen
Sent: Monday, May 22, 2006 11:40 AM
To: Sickafuse, Sharon
Subject: RE: request for compliance check

Sharon - I am waiting on confirmation that the Genentech, Porrino, Spain preapproval EIR has been received and classified by the Foreign Inspection Team. The inspection is not entered into FACTS. If the EIR has not been submitted, I cannot issue the compliance check.

Thanks -

Colleen

From: Sickafuse, Sharon
Sent: Monday, May 15, 2006 3:56 PM
To: Hoyt, Colleen
Subject: RE: request for compliance check

Facilities for drug product manufacturing:

Genentech, Inc.
1 DNA Way
South San Francisco, CA
Domestic registration # - 2917293

Thanks!
Sharon
301-796-1462

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN - 5 2006

William Tester, M.D.
1100 Walnut Street
Suite 701
Philadelphia, PA 19107

b(4)

Dear Dr. Tester:

Between March 27, 2006 and March 31, 2006, and between April 26, 2006 and April 27, 2006 Mr. Mike Rashti, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation protocol E3200, entitled "Phase III Trial of Bevacizumab (NSC 704865), Oxaliplatin (NSC 266046), Fluorouracil, and Leucovorin Versus Oxaliplatin, Fluorouracil, and Leucovorin Versus Bevacizumab Alone in Previously Treated Patients with Advanced Colorectal Cancer." The study of the investigational drug Avastin® (Bevacizumab) Injection was performed for Genentec Inc., the current sponsor.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Mike Rashti during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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 6/1/06
Division of Drug Marketing, Advertising and Communications, CDER

Date: June 1, 2006

Re: **Avastin (Bevacizumab)**
STN BL 125085/74
Comments on draft labeling

In response to your May 31, 2006 electronic mail message, DDMAC has reviewed Genentech, Inc.'s proposed labeling for Bevacizumab and offers the following comments. Comments are provided for the most currently approved WORD version of the draft labeling (as a result of the April 18, 2006, CBE approval for additional language on GI perforation).

Line #	Current PI Statement	Comment
133 - 135	**CLINICAL STUDIES – AVASTIN in Combination with Bolus-IFL** "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	Is it possible to include this data in Table 1 along with the other efficacy results for study 1?

	8.5 months."	
183-192	**CLINICAL STUDIES - AVASTIN In Third Line Metastatic Colorectal Cancer**	This study appears to imply effectiveness for a potential unapproved use (e.g., third line) since the proposed revised indication is for first or second line treatment only. DDMAC suggests that the indication statement be kept broad (e.g., for treatment of patients with metastatic carcinoma of the colon or rectum) and not be specific in stating for first, second or third line which can be better described in the clinical studies section. Please note that DDMAC has not seen the description "Third Line" for a study in a label. DDMAC suggests saying "refractory" or similar wording.

Sickafuse, Sharon

ım:	Sickafuse, Sharon
,nt:	Thursday, May 11, 2006 3:10 PM
To:	Merritt, Babette A
Cc:	Rivera Martinez, Edwin; Cruz, Concepcion
Subject:	request for compliance check

STN: 125085/74

Sponsor: Genentech, Inc.

Product: Bevacizumab

Indication: ——————————————————— b(4)

Action Due Date: June 20, 2006

License Number: 1048

Facilities for drug substance manufacturing:

Genentech, Inc.
1 DNA Way
South San Francisco, CA
Domestic registration # - 2917293

Genentech, Inc.
1000 New Horizons Way
Vacaville, CA
Domestic registration # - 2954595

Genentech Espana
Aptdo. De Correos #85
La Relba, s/n
36410 Porrino (Pontevedra)
Spain

Facilities for drug product manufacturing:

Genentech, Inc.
1 DNA Way
South San Francisco, CA
Domestic registration # - 2917293

Thanks!
Sharon
301-796-1462

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. CBS 5/9/06
Division of Drug Marketing, Advertising and Communications, CDER

Date: May 9, 2006

Re: **Avastin (Bevacizumab)**
STN BL 125085/74
Comments on draft labeling

In response to your consult request dated January 12, 2006, DDMAC has reviewed Genentech, Inc.'s proposed labeling for Bevacizumab and offers the following comments. Comments are provided for the most currently approved WORD version of the draft labeling (as a result of the April 18, 2006, CBE approval for additional language on GI perforation).

Line #	Current PI Statement	Comment
	GENERAL	DDMAC recommends avoiding the use of internal company study titles (e.g., AVF2107g, AVF0780g, E3200 and TRC-0301). We suggest numbering the studies as Study 1, Study 2, and Study 3.
182-183	**AVASTIN in Combination with 5-FU/LV and Oxaliplatin Chemotherapy** _____ _____ _____	DDMAC recommends avoiding the use of the terms "primary" or "secondary" endpoints. Instead, describe only those endpoints that were found to be both statistically and clinically significant.

b(4)

	CLINICAL STUDIES **Table 3**	DDMAC recommends including confidence intervals with the p-values.
214-217	**INDICATIONS AND USAGE**	Does the indications and usage statement include an appropriate level of detail for the population for whom the drug is indicated (e.g., first line treatment and patients previously treated with chemotherapy)? DDMAC notes that the Dosage and Administration section references the previously untreated and previously treated patient populations.
255-259	**WARNINGS – Wound Healing Complications** [redacted]	The first part of this sentence sounds promotional in tone with the words [redacted] DDMAC recommends deleting this part of the sentence. b(4)
694, 697, 708, 717	**ADVERSE EVENTS - Summary Across All Trials** [redacted]	Reference is made to the term "...[redacted]..." when discussing the listed adverse events. Were the adverse events also observed in other non-Genentech sponsored studies? If so, should the adverse events observed in other non-Genentech sponsored studies also be listed in this section? b(4)

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: May 3, 2006

TO: Sharon Sickafuse, Regulatory Project Manager
Jeffery Summers, M.D., Clinical Reviewer
Division of Biologic Oncology Products, HFD-150

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Lauren Iacono-Connors, Ph.D.
Reviewer, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125085\74

NME: No

APPLICANT: Genentech, Inc.

DRUG: Avastin® (Bevacizumab)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of Colorectal Cancer

CONSULTATION REQUEST DATE: February 2, 2006

DIVISION ACTION GOAL DATE: June 20, 2006

PDUFA DATE: June 20, 2006

I. BACKGROUND:

Drug Product:

Bevacizumab, an antiangiogenesis agent, is a recombinant humanized monoclonal antibody (class IgG1) that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Neutralization of VEGF is thought to reduce the vascularization of tumors, and thus, inhibits tumor growth.

Clinical Inspection Summary Report of U.S. Inspections

Bevacizumab is currently approved for the treatment of metastatic colorectal cancer (CRC) as first-line therapy when used in combination with intravenous 5-fluorouracil (5-FU)-based chemotherapy. The sponsor seeks to demonstrate effective treatment for———————— of the colon or rectum, evidenced by a clinically meaningful and statistically significant improvement in overall survival, progression-free survival, and objective response rate, in those subjects receiving Bevacizumab in addition to combination Oxaliplatin/Leucovorin/5-FU (FOLFOX4) chemotherapy. b(4)

The safety and efficacy data submitted to the agency, BLA 125085\74, to support the above indication are drawn in part from a pivotal phase III study, E3200; a multicenter, phase III, randomized, open-label, controlled study. The study called for the enrollment of approximately 880 subjects across the 3 treatment arms.

Protocol E3200:

The phase III study referred to as E3200, in entitled, "Phase III Trial of Bevacizumab (NSC 704865), Oxaliplatin (NSC 266046), Fluorouracil, and Leucovorin Versus Oxaliplatin, Fluorouracil, and Leucovorin Versus Bevacizumab Alone in Previously Treated Patients with Advanced colorectal Cancer." The study seeks to evaluate the overall duration of survival between treatment arms as a primary efficacy endpoint and objective. Secondary efficacy endpoints and objectives were to compare progression-free survival, objective response, and duration of objective response between arms.

Subjects were randomly assigned to one of the 3 treatment groups shown below. Subjects were randomized 1:1:1 and stratified by ECOG performance status (0 vs. ≥1) and prior radiation therapy (yes vs. no). Subjects were to receive a treatment cycle every 2 weeks until disease progression, or were discontinued due to achieving a partial response followed by surgical resection, or were discontinued due to achieving a complete response (followed by 2 additional treatment cycles). No limit was set on the maximum number of treatment cycles.

- **Arm A:**
  - Bevacizumab: 10 mg/kg IV infusion over 90 minutes, DAY 1
  - Oxaliplatin: 85 mg/m^2 IV infusion over 120 minutes, DAY 1
  - Leucovorin: 200 mg/m^2 IV infusion over 120 minutes, DAYS 1 & 2
  - 5-FU: 400 mg/m^2 IV bolus followed by 600 mg/m2 IV infusion over 22 hours, DAYS 1 & 2
- **Arm B:**
  - Oxaliplatin: 85 mg/m^2 IV infusion over 120 minutes, DAY 1
  - Leucovorin: 200 mg/m^2 IV infusion over 120 minutes, DAYS 1 & 2
  - 5-FU: 400 mg/m^2 IV bolus followed by 600 mg/m2 IV infusion over 22 hours, DAYS 1 & 2
- **Arm C:** Bevacizumab: 10 mg/kg IV infusion over 90 minutes, DAY 1

The phase III protocol and its execution by Rogerio Lilenbaum, M.D., Mount Sinai Medical Center in Miami, Florida and William Tester, M.D., Thomas Jefferson University Hospital in Philadelphia, Pennsylvania, are the subjects of this Clinical Inspection Summary. There were a total of 220 study sites within the United States and these sites randomized across three arms a total of 829 subjects (292 FOLFOX4, 293, FOLFOX4+Bevacizumab, 244 Bevacizumab) from November 13, 2001 to April 28, 2003. 23 Subjects were randomized at the Mount Sinai (Miami) center and 13 were randomized at the Thomas Johnson University Hospital center in Philadelphia.

II. RESULTS:

Name	City, State	Protocol	Inspection Dates	EIR Received Date	Final Classification
Rogerio C. Lilenbaum, M.D.	Miami Beach, FL	E3200	3/2/06 - 3/8/06	3/27/06	VAI-No RR
William J. Tester, M.D.	Philadelphia, PA	E3200	3/27/06 – 4/27/06	Pending PHI-DO	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # E3200

1. **Rogerio C. Lilenbaum, M.D.**
Mount Sinai Medical Center CCOP
Cancer Center
4306 Alton Road
Miami Beach, FL 33140 US

a. What was inspected?

The study records of 8 of the 20 subjects enrolled into the phase III study, and under the care of Dr. Lilenbaum, were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these 8 subjects the record audit included comparison of source documentation to CRFs with particular attention paid to eligibility criteria satisfaction, confirmation of diagnosis. The FDA investigator also assessed the date and cause of death, and any SAEs and AEs and informed consent forms.

b. Limitations of inspection: None

c. General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. With respect to the efficacy data, no discrepancies were observed. Source data were audited for 8 subjects.

In addition to the routine clinical investigator compliance program assessments, the investigator had the site determine the location of the baseline and complete follow-up series (baseline and every 8 weeks thereafter while on study) of radiology imaging scans used for evaluation of tumor response. A listing of these images and there location were provided to the FDA as an attachment to the EIR. This added inspection activity was at the direction of the DSI reviewer in support of the review division Medical Officer. The list of scan locations will be forwarded to the review division Medical Officer upon request.

A Form FDA 483 was issued citing 4 major inspectional observations.

Observation 1. An investigation was not conducted in accordance with the investigational plan.

a. According to the Protocol Transmittal Form, dated 12/5/01, submitted to the Mt. Sinai Medical Center IRB by the initial Clinical Investigator, Dr. Davila, "Following approval of the informed consent document, an accurate translation of the approved consent document must be submitted to the IRB. If a non-English speaking subject is unexpectedly encountered, investigators must rely on an oral translation. In this case, a 'short form' written consent document in the language the subject understands must be used to document that the elements of informed consent as required by 21 CFR 50 and 46 CFR 46 were translated and presented orally." The Protocol Transmittal Form clearly indicated that the investigator expected Spanish speakers to be candidate subjects in the study, E3200. However, the entire consent form was never translated into Spanish nor forwarded to the local IRB for approval. The IRB did approve a Spanish language "short form" for use along with a Spanish speaking translator to support oral consent. This short form was an addendum to the English ICD, provided for signature of the subject and stated essentially in written Spanish that the subject understood the contents of the English ICD on the study presented to them orally. The following subjects were consented using the above described, non-protocol directed, consenting procedures: 33003, 33035, 33124, 33181.

b. With respect to subject 33124 the following protocol-required tests were not done at the C7 study visit/treatment interval (2/20/03); SGOT, SGPT, alkaline phosphatase, and bilirubin.

Observation 2. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

a. The E3200 Treatment Summary Form for subject 33124 states that the treatment was ended due to, "tx regimen found to be inferior as per ECOG." In contrast, Dr. Lilenbaum's Consultation Report dated 9/17/03 states that, "the treatment was halted because of progressive proteinuria."

b. Subject 33124 was to have been dose reduced at the C7 cycle on 2/20/03 from 10 mg/kg to 5 mg/kg in response to a 24 hour protein result of 1,110 mg on 2/10/03. The full dose was given in error. However, the E3200 Treatment Summary Form dated 3/17/03 states that dose modifications or additions/omissions to protocol treatment were initiated as planned.

c. Scheduled treatment on 3/20/02 for subject 33003 was held until 3/27/02 without documented justification since there were no protocol defined toxicities requiring that the treatment be held. This deviation was not documented in the E3200 Treatment Summary Form.

d. On 4/24/03 subject 33202 reported infusion pump leakage during treatment. The volume of drug "not administered" was not estimated nor was the incident reported in the E3200 Treatment Summary Form.

Observation 3. Failure to report promptly to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug.

a. The protocol requires reporting within 7 days of grade 3 unrelated or unlikely adverse events if subject is hospitalized.
    i. Subject 33084 experienced an infection with grade 3 neutropenia from 10/17/02 to 10/20/02, however, the NCI Adverse Event Expedited Report was not submitted until 12/26/02.

ii. Subject 33035 experienced a grade 4 bowel obstruction with a start date of 3/11/02. The Adverse Event Report was prepared on11/11/02. [Observation made Post-Inspection.]

Observation 4. Investigational drug disposition records are not adequate with respect to use by subjects.

a. The study drug, Bevacizumab required storage at temperatures of 2-8 degrees Celsius [35.6 – 46.4 degrees Fahrenheit]. Review of main pharmacy temperature monitoring records specific to the refrigerator holding the study drug show sporadic storage temperatures of 47 degrees Fahrenheit and above. Sample temperature deviations are provided below:
   i. 12/16/01 to 12/19/01 temperature logs showed temperature ranging between 47 and 49 degrees Fahrenheit.
   ii. 2/20/02 to 2/21/02 temperature logs showed temperature ranging between 47 and 48 degrees Fahrenheit.
   iii. No temperature records were available from 3/2/02 to the end of patient treatment in 2003.

b. With respect to subject 33118 medication administration records shows the administration of Bevacizumab at 700 mg/sodium chloride 0.9% diluent with a total volume of 30 mL on both 2/19/03 and 3/5/03. Seven 4 mL vials (bevacizumab 25 mg/mL) for each drug administration were dispensed from the same lot, R9812A1. Therefore the drug volume for each dose would be 28 mL total volume. Other medication records for subject 33118 show either a 100 mL total volume of dosed material (assumed study drug, neat, plus saline diluent, as per protocol) or just the saline volume alone. It is not clear from these records why there are volume dosing discrepancies.

c. With respect to study subject 33150, study drug administration shows a volume of 40 cc for bevacizumab, and a total drug dose of 960 mg. However, the lot used for source material was packaged as 10mg/mL, therefore the volume of study drug alone should have been 96 cc not 40 cc.

d. **Assessment of data integrity:** The data from Dr. Lilenbaum's site, associated with protocol E3200, submitted to the agency in support of efficacy supplement BLA 125085\74, is reliable.

2. **William J. Tester, M.D.**
Jefferson Cancer Network
1100 Walnut St. Suite 701
Philadelphia, PA 19107 US

a. **What was inspected?**

The study records of 9 of the 13 subjects enrolled into the phase III study were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these 9 subjects the record audit included comparison of source documentation to CRFs with particular attention paid to eligibility criteria satisfaction, confirmation of diagnosis. The FDA investigator also assessed the date and cause of death, and any SAEs and AEs and informed consent forms.

b. **Limitations of inspection:** None

c. General observations/commentary

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. With respect to the efficacy data, no discrepancies were observed. Source data were audited for 9 subjects. CRFs were assessed for data consistency with the source documents. Adverse events (AEs) and serious adverse events (SAEs) were properly documented and were sent to the sponsor and to the Institutional Review Board (IRB) in a timely manner. Only minor record keeping discrepancies were observed, and this was verbally discussed with the study management at the conclusion of the inspection; a Form OSA-10, Thomas Jefferson University Report of Averse Event Reaction, for the IRB for 5 subjects (# 32501, 32572, 32077, 32271, and 32269) were signed but not dated by the clinical investigator. No Form FDA 483 was issued.

In addition to the routine clinical investigator compliance program assessments, the investigator obtained copies (electronic/digital/hard media) of the baseline and complete follow-up series (baseline and every 8 weeks thereafter while on study) of radiology imaging scans used for evaluation of tumor response and obtained the corresponding copies of the source documents for findings/interpretation of each image. This added inspection activity was at the direction of the DSI reviewer in support of the review division Medical Officer. Radiography scans and interpretive source documents were collected by the FDA field investigator for an undetermined number of study subjects enrolled at this site and will be forwarded to the DSI along with the pending EIR. The EIR will also note if radiography images or source documentation supporting their interpretation were missing. These materials will be forwarded to the review division Medical Officer upon receipt unless otherwise directed.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on the preliminary EIR and communication from the field investigator, Mr. Mike Rashti. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. **Assessment of data integrity:** The data from Dr. Tester's site, associated with protocol E3200, submitted to the agency in support of efficacy supplement BLA 125085\74, is reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The sites inspected, that of Dr. Lilenbaum and Dr. Tester, were found to generally adhere to the applicable regulations governing the conduct of clinical investigations; with noteworthy observations cited on a Form FDA 483 for Dr. Lilenbaum's site. Those observations revealed a number of protocol violations that should not impact the quality of the primary efficacy data generated by the site. Observations included consenting process issues, some minor record keeping deficiencies, and several delinquent AE reporting actions.

The primary efficacy data generated by the inspected sites, that of Dr. Lilenbaum and Dr. Tester, and submitted to the agency in support of BLA 125085\74, may be considered reliable.

Observations noted above are based in part on the preliminary communications provided by one of the field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIR and the supporting inspection evidence and exhibits.

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Monday, April 24, 2006 3:39 PM
To: 'Lisa Schain'
Subject: IR request for STN 125085/74

During FDA's review of the narratives provided for subjects on the FOLFOX + Bevacizumab and Bevacizumab monotherapy arms, many inconsistencies between the narratives and respective subject CRFs have been identified. Please provide a detailed description of the manner in which the narratives were generated, and most importantly the steps that Genentech as the sponsor of this study employed to verify the completeness and veracity of the narratives provided to the FDA for review. Please submit this information by May 17, 2006.

Please submit a revised red-line label in WORD due to last Tuesday's approval of the GI perforation CBE (i.e, your proposed changes on the most recently approved labeling). I will need to have this label by next week. Please send as an email attachment with a follow-up amendment to the supplement. The follow-up amendment will also need to have the label in SPL.

Any questions, please call. I'm in the office Mon., Tue., and Thur.

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

Memorandum

Date: **April 4, 2006** SKS

From: **Sharon Sickafuse, M.S., DBOP/OODP/CDER**

To: **STN 125085/74**

Subject: **Mid-Cycle Meeting**

PARTICIPANTS:

CDER/OODP: **Jeff Summers, Joe Gootenberg, Pat Keegan, Karen Weiss**

CDER/OBS: **Yuan-Li Shen**

The mid-cycle review meeting was held April 4, 2006, to discuss the status of the reviews for the Genentech Bevacizumab priority sBLA 125085/74 that expands the indication to include 2nd line treatment of colorectal cancer.

Dr. Jeff Summers gave a presentation of the supplement and the status of his review.

Sickafuse, Sharon

STN 125085/74

m: Sickafuse, Sharon
t: Friday, March 24, 2006 4:31 PM
o: 'lschain@gene.com'
Subject: this week's IR request re the Bev PAS

For subjects 33038, 34002, 32526 and 32045 please provide the reason for which the Thrombosis/embolism adverse events were coded on the E3200 Toxicity Form as Venous thromboembolism, as no documentation of the venous nature of the adverse event is present in the CRF. Please provide an explanation why Subject 32526 is coded as having incurred a Thrombosis/embolism adverse event sub-classified as Venous thromboembolism when the CRF states this was a femoral artery thrombus.

If the information used to code the Thrombosis/embolism adverse events are not available in the CRFs provided for review, or are incorrectly coded, please discuss the reliability of the Adverse Event data set regarding Thrombosis/embolism events coded as Venous thromboembolism, and the reliability in general of the Adverse Event data set. Please provide a tabular listing of each subject experiencing a Thrombosis/embolism adverse event that was coded as Venous thromboembolism and the source data used for the determination of that coding and the CRFs for the respective subjects.

Sickafuse, Sharon

rom: Sickafuse, Sharon
ht: Friday, March 17, 2006 4:56 PM
To: 'lschain@gene.com'
Subject: this week's IR for Bev PAS STN 125085/74

FDA is unable to find information in the CRFs regarding individual dates of administration of chemotherapy. The only information that appears to be available is the date of initiation and cessation of chemotherapy and the total number of cycles administered. Please describe the manner in which FOLFOX 4 chemotherapy or any component of the FOLFOX 4 chemotherapy was documented as having been administered on particular cycle days or dates in the CFRs.

Sickafuse, Sharon

om: Sickafuse, Sharon
nt: Friday, March 10, 2006 2:44 PM
To: 'bell.lisa@gene.com'
Subject: FW: more IR for STN 125085/74

Attachments: March 10 IR.doc

From: Sickafuse, Sharon
Sent: Friday, March 10, 2006 2:35 PM
To: 'lschain@gene.com'; 'lisa.bell@gene.com'
Subject: more IR for STN 125085/74

March 10 IR.doc
(34 KB)

March 10, 2006, information request for STN 125085/74

1. Please clarify if subjects with advanced or metastatic CRC who had received 5-FU and irinotecan, but had not progressed could go on study. Please identify the section of the protocol that specifies that eligibility is limited solely to subjects who had experienced prior progression. Please provide the unique subject identifiers and the duration of chemotherapy received prior to going on study for the subjects who went on study with advanced or metastatic disease and had not progressed or state the reason why you are unable to provide this information.

2. Your February 28, 2006, response to question 6a of the February 17, 2006, FDA letter states that the adverse event reporting requirements were not changed in amendments 2, 3, 5, 7, or 8. Please clarify if the ASAEL was revised with these amendments, therefore entailing changed reporting requirements.

3. Please clarify the reasons for the following as noted in the E3200 CSR Table 4 page 61 and Table 14.1/4. In addition, please identify by treatment arm the number of subjects who were not assessed for each of the deviation types.

    a. Major protocol deviations were only assessed in 710 of 806 subjects who received protocol therapy.

    b. Minor protocol deviations were only assessed in 713 of 806 subjects who received protocol therapy.

    c. Stratification errors were only assessed in 652 of 806 subjects who received protocol therapy.

    d. Other protocol deviations were only assessed in 567 of 806 subjects who received protocol therapy.

4. Please describe in detail the mechanism to determine and document that subjects enrolled on Study E3200 met the study eligibility criteria. Please address the following specific eligibility issues:

    a. Confirmation that enrolled subjects had received prior 5-FU and irinotecan chemotherapy.

    b. Confirmation that enrolled subjects had histologically confirmed adenocarcinoma of the colon and rectum documented within 4 weeks prior to randomization.

c. In addition, please provide the number of subjects by treatment arm who had histologically confirmed adenocarcinoma of the colon and rectum documented within 4 weeks prior to randomization as indicated in the ECOG Pathology Material Submission Form.

5. Please provide the number of subjects by treatment arm who had histologically confirmed adenocarcinoma of the colon and rectum documented within 4 weeks prior to randomization as indicated in the ECOG Pathology Material Submission Form.

5 6. With regard to copies of tumor-assessment imaging data requested under item 7 of the February 17, 2006, filing/deficiency letter, pleased be advised that due to time constraints, FDA will be unable to review any imaging data received after April 14, 2006.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125085/74

FEB 17 2006

Genentech, Incorporated
Attention: Robert L. Garnick, Ph.D.
Senior Vice President, Regulatory Affairs, Quality and Compliance
1 DNA Way, MS# 242
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 December 15, 2005, 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 June 20, 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:

1. Ninety-eight confirmed complete response and partial response subjects were identified in the RESPSUMM data set. Seventy of the subjects had no data collected for non-protocol anti-tumor therapy. For the 28 subjects with data available, the following subjects received anti-tumor therapy before confirmed progression: 32014, 32123, 32126, 32172, 32299, 32351, 32395, 32449, 32465, 32559, 33019, 33073, and 33170. Please provide, or state the reason why you are unable to provide, narrative information for each specific subject, furnishing the reason(s) for anti-tumor therapy prior to documentation of progressive disease.

2. The RESPSUMM dataset reveals that 647 out of 829 subjects have missing data regarding non-protocol anti-tumor therapy. Of the 137 subjects who are documented in the database as having received non-protocol anti-tumor therapy, 65 of these received the non-protocol anti-tumor therapy prior to disease progression. Please provide, or state the reason why you are unable to provide, a detailed analysis on "non-protocol anti-tumor therapy" administered by treatment arm to include the following:

   a. The number of subjects with missing data.

   b. The number of subjects who received non-protocol anti-tumor therapy.

c. The number of subjects who received non-protocol anti-tumor therapy prior to documentation of progressive disease.

d. The nature of the non-protocol anti-tumor therapy received prior to documentation of progressive disease.

e. The reasons for administration of non-protocol anti-tumor therapy prior to documentation of progressive disease.

f. An analysis of the validity of the progression-free survival (PFS) data based on the evidence of non-protocol anti-tumor therapy administered to subjects prior to determination of progressive disease and the extent of missing data regarding non-protocol anti-tumor therapy.

3. Page 124, paragraph 4 of the E3200 clinical study report states: "Of note, Genentech Clinical Scientist review determined that 37 of 70 patients (52.9%) in the FOLFOX4 + Bevacizumab arm reporting adverse events leading to discontinuation of Bevacizumab reported events that were not specified in the protocol as requiring Bevacizumab discontinuation. The proportion of patients who discontinued all protocol therapy for toxicity (as collected on the Treatment Summary Form and shown in Table 2) was similar between the principal arms (23.6% FOLFOX4; 22.5% FOLFOX4 + Bevacizumab). These data suggest that the proportion of patients in the FOLFOX4 + Bevacizumab arm with events leading to discontinuation of Bevacizumab for toxicity as reported on the retrospectively collected E3200 Bevacizumab Dose Modification Form may include patients with discontinuations of all protocol therapy for toxicity."

   Please utilize the dates that Bevacizumab therapy was discontinued in the retrospective E3200 dose modification form and the dates that FOLFOX 4 was discontinued from the E3200 CRT data sets to determine the percentage of patients who had Bevacizumab discontinued but continued to receive FOLFOX 4 chemotherapy. Please provide the specific patient ID for each patient who had Bevacizumab discontinued but continued to receive FOLFOX 4 chemotherapy.

4. Please provide in tabular format, utilizing the Case Report Forms (CRFs) and CRT datasets, the incidence of $\geq$ Grade 3 neurotoxic events for each treatment arm by cycle and by cumulative cycle number.

5. The E3200 clinical study report states that subjects were included on an Expanded Participation Program (EPP) component of the E3200 study, however, the study report does not adequately describe this aspect of the trial. Subjects enrolled on the EPP did not have tumor measurements recorded in the TUMORI dataset provided. Please provide the following regarding the EPP component of the study:

a. A detailed description of the EPP component of the study, including the differences in data acquisition and safety reporting between the subjects enrolled in E3200 and the EPP part of the E3200 trial.

b. The rationale for the differences between EPP and non-EPP subjects in the conduct of the E3200 trial.

c. A detailed description of the manner in which response and PFS data were determined by the centralized ECOG review process for the EPP subjects.

d. A sensitivity analysis on all efficacy determinations for the secondary endpoints in which the subjects enrolled under the EPP are excluded from analysis.

6. The E3200 clinical study report states that the adverse event onset dates were not collected on the toxicity case report form and that instead the reporting period (ranging from 1 to 3 months) during which the event occurred was recorded. Please provide a detailed description of the history and mechanics of adverse event acquisition to include:

a. The distinct periods (start and end dates) during which adverse events were collected with the respective varying frequencies of acquisition.

b. The rationale provided in the protocol and protocol amendments for justification of the adverse event reporting frequencies and the reasons for any changes.

c. A tabular format by treatment arm of the proportion of total number of adverse events recorded using each "reporting period duration".

d. The manner and frequency in which subjects were queried, i.e., open ended versus specific questions.

7. Please supply the baseline and complete follow-up series of radiology imaging scans used for evaluation of tumor response from Thomas Jefferson University, Missouri Baptist and Vanderbilt University for the following subjects: 33004, 33028, 33089, 33119, 32126, 32141, 32269, 32349, 32391, 32572, 32329, 32350, and 32412.

8. The AE.xpt data set (adverse events from all sources) does not appear to allow separation/identification of adverse events that were reported in an identical fashion in all treatment arms (E3200 Toxicity form) from those adverse events reported through NCI AdEERS which had different reporting requirements depending on the study arm. Please provide clarification on how the AE.xpt data set is organized to allow for the differentiation of adverse events based on the E3200 toxicity form from those reported through NCI AdEERS.

If the dataset is not organized to allow differentiation of the reporting mechanism of the adverse events, please provide a dataset derived from the E3200 toxicity form (or other CRF adverse event collection data/forms) for all adverse events that were reported using the same reporting requirements.

9. Please perform and provide the results of the following analyses:

   a. The frequency of imaging assessments for all subjects by treatment arm including mean, median, and quartiles.

   b. The frequency of imaging assessments after a documented objective response for all subjects with an objective response by treatment arm including mean, median, and quartiles.

10. Please provide Protocol Addendum 1.

11. Please confirm that the (RSPASDT) data column in the RESPSUME dataset was obtained from the ECOG Internal Nonadjuvant Solid Tumor Response Coding Form (RECIST). If this data column does not represent the date of tumor assessment as determined from the ECOG Internal Nonadjuvant Solid Tumor Response Coding Form, please provide additional clarification on coding of tumor assessment dates in the data sets provided.

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 yours,

Patricia Keegan

Patricia Keegan, M.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/S. Sickafuse
DBOP BLA file (hard copy)

History: Sickafuse: 2-3-06:2-13-06: K. Townsend: 2.14.2006:sks:2-16-06: K. Townsend: 2.17.2006

File Name: (S:Sickafuse\Bevacizumab\efficacy supplements\125085_74\filing letter.doc)

Division	Name/Signature	Date
OODP/DBOP	Karen D Jones for S. Sickafuse	2-17-06
DBOP	P. Keegan	2-17-06
DBOP	Kelly Townsend	2/21/06

Sickafuse, Sharon

m: Sickafuse, Sharon
t: Wednesday, February 08, 2006 4:29 PM
o: 'lschain@gene.com'
Subject: Bev PAS - another IR

Request to Genentech for additional information for BLAs 125085.74

In order for a timely review of this application, please provide the requested data as soon as possible and no later than March 3, 2006:

The AE.xpt data set (Adverse events from all sources) does not appear to allow separation/identification of adverse events that were reported in an identical fashion by treatment arm (E3200 Toxicity form) from the adverse events reported through NCI AdEERS that had different reporting requirements depending on the study arm. Please provide clarification on how the AE.xpt data set is organized to allow for the differentiation of AEs based on the E3200 toxicity form from those reported through NCI AdEERS. If the data set is not organized to allow differentiation of the reporting mechanism of the AEs, please provide a data set derived from the E3200 toxicity form (or other CRF AE collection data/forms) for all adverse events that were reported using the same reporting requirements.

Sickafuse, Sharon

m:	Sickafuse, Sharon
it:	Friday, February 03, 2006 12:23 PM
To:	'lschain@gene.com'; 'lisa.bell@gene.com'
Subject:	IR for Bev colorectal PAS STN 125085/74

In order for a timely review of this application, please provide the requested data as soon as possible and no later than February 28, 2006:

1. 98 confirmed CR and PR subjects were identified in the RESPSUMM data set. 70 of the subjects had no data collected for non-protocol anti-tumor therapy. For the 28 subjects with data available, the following subjects received anti-tumor therapy before confirmed progression: 32014, 32123, 32126, 32172, 32299, 32351, 32395, 32449, 32465, 32559, 33019, 33073, and 33170. Please provide, or state the reason why you are unable to provide, narrative information for each specific subject furnishing the reason(s) for anti-tumor therapy prior to documentation of progressive disease.

2. The RESPSUMM data set reveals that 647 out of 829 subjects have missing data regarding non-protocol anti-tumor therapy. Of the 137 subjects who are documented in the database as having received non-protocol anti-tumor therapy, 65 of these received the non-protocol anti-tumor therapy prior to disease progression. Please provide, or state the reason why you are unable to provide, a detailed analysis on "non-protocol anti-tumor therapy" administered by treatment arm to include the following:

   a. The number of subjects with missing data.

   b. The number of subjects who received non-protocol anti-tumor therapy.

   c. The number of subjects who received non-protocol anti-tumor therapy prior to documentation of progressive disease.

   d. The nature of the non-protocol anti-tumor therapy received prior to documentation of progressive disease.

   e. The reasons for administration of non-protocol anti-tumor therapy prior to documentation of progressive disease.

   f. An analysis of the validity of the PFS data based on the evidence of non-protocol anti-tumor therapy administered to subjects prior to determination of progressive disease and the extent of missing data regarding non-protocol anti-tumor therapy.

3. Page 124, paragraph 4 of the E3200 study report states:

   Of note, Genentech Clinical Scientist review determined that 37 of 70 patients (52.9%) in the FOLFOX4 + bevacizumab arm reporting adverse events leading to discontinuation of bevacizumab reported events that were not specified in the protocol as requiring bevacizumab discontinuation. The proportion of patients who discontinued all protocol therapy for toxicity (as collected on the Treatment Summary Form and shown in Table 2) was similar between the principal arms (23.6% FOLFOX4; 22.5% FOLFOX4 + bevacizumab). These data suggest that the proportion of patients in the FOLFOX4 + bevacizumab arm with events leading to discontinuation of bevacizumab for toxicity as reported on the retrospectively collected E3200 Bevacizumab Dose Modification Form may include patients with discontinuations of all protocol therapy for toxicity.

   Please utilize the dates that Bevacizumab therapy was discontinued in the retrospective E3200 dose modification form and the dates that FOLFOX 4 was discontinued from the E3200 CRT data sets to determine the percentage of patients who had Bevacizumab discontinued but continued to receive FOLFOX 4 chemotherapy. Please provide the specific patient ID for each patient who had bevacizumab discontinued

but continued to receive FOLFOX 4 chemotherapy.

4. Please provide in tabular format, utilizing the Case Report Forms and CRT data sets, the incidence of ≥ Grade 3 neurotoxic events for each treatment arm by cycle and by cumulative cycle number.

5. The E3200 CSR states that subjects were included on an Expanded Participation Program (EEP) component of the E3200 study, however, the study report does not adequately describe this aspect of the trial. Subjects enrolled on the EPP did not have tumor measurements recorded in the TUMORI data set provided. Please provide the following regarding the EPP component of the study:
   a. A detailed description of the EPP component of the study, including the differences in data acquisition and safety reporting between the subjects enrolled in E3200 and the EPP part of the E3200 trial.
   b. The rationale for the differences between EPP and non-EPP subjects in the conduct of the E3200 trial.
   c. A detailed description of the manner in which response and progression free survival data were determined by the centralized ECOG review process for the EPP subjects.
   d. A sensitivity analysis on all efficacy determinations for the secondary endpoints in which the subjects enrolled under the Extended Participation Program are excluded from analysis.

6. The E3200 CSR states that the adverse event onset dates were not collected on the Toxicity CRF and that instead the reporting period (ranging from 1 to 3 months) during which the event occurred was recorded. Please provide a detailed description of the history and mechanics of adverse event acquisition to include:
   a. The distinct periods (start and end dates) during which adverse events were collected with the respective varying frequencies of acquisition.
   b. The rationale provided in the protocol and amendments for justification of the adverse event reporting frequencies and the reasons for any changes.
   c. Provide in a tabular format by treatment arm the proportion of total number of adverse events recorded using each "reporting period duration".
   d. The manner and frequency in which subjects were queried, i.e., open ended versus specific questions.

7. Please supply the baseline and complete follow-up series of radiology imaging scans used for evaluation of tumor response from Thomas Jefferson University, Missouri Baptist and Vanderbilt University for the following subjects: 33004, 33028, 33089, 33119, 32126, 32141, 32269, 32349, 32391, 32572, 32329, 32350, 32412.

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)	Not required

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)	Not required
◻ 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 applicable 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
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)	not required

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
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)	
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 electonic datasets complete & usable?		BiMo sites identified?		
E3200	(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	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?

YES

Is an Advisory Committee needed?

NO

Recommendation (circle one): (File) RTF

Reviewer: [signature] Type (circle one): (Clinical) Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [signature] 2/1/06 Division. Director: [signature] 2/1/06
(signature/ date) (signature/ 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: 125085/74 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 1-31-06 Committee Recommendation (circle one): (File) RTF

RPM: Sharon Sickafuse 1-31-06
(signature/date)

Attachments:

- ☐ 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 Product Part A Page 2

Examples of Filing Issues	Yes?	If not, 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? no
If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? yes # 17

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: Sukafuse 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 applicable (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	NA
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	NA
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	

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 electonic datasets complete & usable?		BiMo sites identified?		
E3200	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	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] 1-31-06 Type (circle one): Clinical Clin/Pharm (Statistical)
(signature/ date)

Concurrence:

Branch Chief: _____ Division. Director: Alaka Chakravarty 1/31/06
(signature/ date) (signature/ date)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JAN 20 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:

SUBMISSION TRACKING NUMBER (STN) BL 125085/74 has been assigned to your recent supplement to your biologics license application for Bevacizumab received on December 19, 2005, to provide for treatment of patients with metastatic colorectal carcinoma previously treated with 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
DBOP BLA file (hard copy)

History: K. Townsend: 1.17.2006: 1.18.2006

File Name: N:\DBOP\STN 2006\125085.74.PAS.doc

Office	Name/Signature	Date
DBOP	Sickafuse	1-19-06
OODP/DBOP	Karen D Jones	1-20-06
OODP/DBOP	Kelly LaDonna	1-25-06

BLA/NDA/PMA
Review Committee Assignment Memorandum

STN: 125085/74

☒ 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	12-19-05
	Reviewer	Admin/Regulatory		
		Product*		
	Reviewer	Product*		
	Reviewer	Product		
Jeff Summers		Clinical	P. Keegan	12-9-05
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
Yuan Lee Shen	Reviewer	Biostatistics	M. Kohmann	1-4-06
Lauren Iacono-Connor	Reviewer	BiMo	L. Ball	1-12-06
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
Carole Broadnax	Reviewer	Labeling	M. Kiester	1-12-06
		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 — Name Printed / Signature

1-12-06 — Date

Memo entered in RMS by: KA Date: 1/17/06 QC by: _____ Date: _____

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

Memorandum

Date: January 12, 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: Provide for treatment of patients with metastatic colorectal carcinoma previously treated with chemotherapy

To: STN 125085/74

The review status of this file is designated to be:

☐ Standard (10 mon.) ☒ Priority (6 mon.)

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

Memorandum

Date: April 5, 2005 SKS

From: Sharon Sickafuse, CDER/ODE6/DRMP

To: IND 7023

Subject: March 10, 2005, pre-sBLA teleconference with Genentech regarding ECOG study E3200

Teleconference Date: March 10, 2005

Teleconference Requestor: Genentech, Inc.

Product: Bevacizumab

Proposed Use: Treatment of colorectal cancer

Teleconference Purpose: Discuss proposed content of sBLA for ECOG study E3200, "Phase 3 Trial of Bevacizumab, Oxaliplatin, 5FU, and Leucovorin versus Chemotherapy Alone Versus Bevacizumab Alone in Previously Treated Patients with Advanced Colorectal Cancer. Teleconference package is amendment 523.

Background: Draft FDA responses to Genentech's questions were faxed to Genentech on March 2, 2005. Genentech's questions, FDA draft responses, and discussion between FDA and Genentech are captured below.

1. *Based on the significant survival results and the safety profile observed with bevacizumab in Study E3200, Genentech believes that the results from this pivotal trial are sufficient to support an sBLA to extend the current indication of Avastin to the following:*

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b(4)

Does the Agency agree that Study E3200 can form the basis for this sBLA? Does the Agency agree with the proposed indication statement?

FDA Response:

- The Agency cannot comment upon the indication statement prior to review of the primary data.

- Data from AVF2107g (1st line), E3200 (2nd line), and ———— will be used in the evaluation of this indication. b(4)

Discussion:
Genentech stated that they will provide in the sBLA clinical study reports for 2107g and E3200 and a summary report from NCI on study———— b(4)

2. *Does the Agency agree with Genentech's proposal for submission of the clinical study report, patient narratives, case report forms, and case report tabulations?*

FDA Response: No. Please see the following table:

	GNE Proposal	FDA
CRFs	Pts w/narratives	Pts w/narratives
Narratives	Deaths < 30 d not due to PD, related deaths > 30 d. AEs leading to discontinuation AEs leading to dose reduction GI perforation, fistula formation Arterial events Gr 4 Events-proteinuria, HTN, diarrhea Gr 3-4 Events-venous thrombosis, CHF, hemorrhage, abn healing or bleeding AdEERs Reports	Please include Gr 3 proteinuria. Please include patients with second malignancies. Please include Gr 3 and 4 neuropathy leading to discontinuation of oxaliplatin.
Safety Update	None	Pts currently on study included in initial data submission (see item 6)

- Please confirm that narratives will be provided for approximately 40% of patients.
- Please state the availability of dosing and dose modification information.
- We acknowledge that pharmacokinetic information will not be provided.
- Please confirm that all protocols, protocol amendments, data monitoring committee charter(s), data monitoring committee minutes and analyses, statistical analysis plans, and amendments to the statistical analysis plan will be submitted.

Discussion:
FDA inquired about the relationship between AdEERs reports and patient narratives because of a concern that AdEERs narratives are often incomplete. Genentech stated that the patient narrative is drawn from the AdEERs report and the CRF.

Genentech agreed to provide narratives for patients with Grade 3 proteinuria and the patients with a second malignancy (gastric cancer). Genentech and FDA agreed that Genentech would provide narratives for all patients who discontinue oxaliplatin, regardless of cause. Genentech confirmed that narratives will be provided for approximately 40% of patients.

Regarding the issue of dose and dose modification information, ECOG stated that they are collecting dosing information on only those patients who had modifications of the Bevacizumab dose or discontinued Bevacizumab. FDA said this was acceptable and asked Genentech to confirm the other patients had the planned Bevacizumab dose as per protocol.

Genentech confirmed that all protocols, protocol amendments, statistical analysis plans (SAPs), and amendments to the SAPs will be submitted in the sBLA. ECOG stated that they can provide general policies for the data monitoring committee (DMC), but not a specific charter for this study because there isn't one. ECOG clarified that the DMC minutes consist of the topics discussed and the final conclusion, but not the actual discussion that took place. These minutes will be included in the sBLA.

3. *Does the Agency agree with Genentech's proposal for basing the study conclusions for E3200 in the sBLA on two sources (the November 2004 interim analysis results and the analyses presented in the clinical study report) as described in Section 10.1.1?*

FDA Response:

- The study conclusions for E3200 submitted in the sBLA should be those agreed to in the final SAP.
- DMC minutes and analyses should be provided as part of the sBLA.
- Please provide the rationale behind your intent to provide two conclusions.

Discussion:

Genentech confirmed that the study conclusions for E3200 will be based on the analyses in the final SAP. They will provide the DMC minutes as discussed in item 2. Genentech clarified that while they are using two sources for the survival endpoint, information in the sBLA on the November 2004 interim analysis will only state that the results of the interim analysis showed statistical significance.

4. *Does the Agency agree with Genentech's proposals for the Summary of Clinical Efficacy and Summary of Clinical Safety to be provided?*

FDA Response:
No. Please see table below.

	GNE Proposal	FDA
ISS	E3200 Integrated GNE trials-excluding extension studies _____	E3200 Integrated GNE trials-excluding extension studies Integration of GNE & E3200 single agent experience
ISE	E3200 AVF2107g AVF2192g	E3200 AVF2107g AVF2192g AVF0780g

b(4)

In the initial Bevacizumab BLA, information was provided on 157 patients who received single agent therapy. E3200 will provide additional information on 239 patients who received single agent Bevacizumab. Please provide safety analyses for the 239 patients on E3200 as well as an ISS for these 239 patients with the 157 other patients who also received single agent Bevacizumab.

Discussion:
FDA would like to evaluate the toxicity profile of single agent Bevaciuzmab using a larger safety database. This will be facilitated by the integration of the single agent experience in E3200 with other Genentech studies.

FDA also plans to compare the toxicity profile of Bevaciuzmab versus Bevacizumab plus chemotherapy within E3200

Genentech/ECOG expressed reluctance to provide an ISS for the _____ They believe that the most relevant comparison is that of Bevacizumab to Bevacizumab plus chemotherapy within E3200. Genentech agreed to provide a proposal for the integration of the _____

b(4)

In response to an FDA question, ECOG clarified that the adverse event terms used were from the NCI-CTC Version 2. FDA noted that this makes integration easier than if the Genentech studies and the E3200 study used different adverse event terms.

5. *Does the Agency agree with Genentech's plans to submit the application in eCTD format?*

FDA Response: Yes. However, please contact Joseph Montgomery and Gary Gensinger to obtain detailed information concerning the submission. A browser to review the document would be most helpful.

6. *Genentech does not intend to submit a Safety Update to the sBLA. Does the Agency agree?*

FDA Response: As of 12-04, 30 patients were receiving active therapy on Arms A and B. Please include information on deaths, discontinuations, expedited reports, serious adverse events, adverse events, and patient narratives (as appropriate) for these patients as of 6-05 in the sBLA. It is not necessary to integrate this information into your safety analyses.

Discussion: Genentech stated that they are not using 12-04 as the date of database cut-off. The database cut-off will be midsummer, but no exact date has been set. It is likely that there will be no patients on active therapy at that point.

Genentech agreed to provide the requested data if patients are still on active therapy by database cut-off. FDA asked Genentech to highlight any areas in which they could not collect the data.

7. *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?*

FDA Response: Yes.

Additional FDA Comments:

1. When submitting the final study report for E3200, please note in your cover letter that this will address Post-Marketing Commitment 17.

   Genentech will do this.

2. Please provide the eligibility checklist used by ECOG. Please state whether information collected on the checklist will be submitted in the sBLA.

   Genentech agreed to fax the eligibility checklist to Dr. Maher. They were not planning on submitting data from the checklist as part of the sBLA.

3. The On-Study Form (ECOG case report forms) collects information on current tumor sites and prior adjuvant therapy (yes/no). In Attachment E slide 13, you provide information on the first line and adjuvant therapy received. Please state what information, in addition to that in the case report forms, was collected and what will be included in the sBLA.

   Genentech stated that this information was from the eligibility checklist. They will provide a blank checklist. Genentech intends to include only information on first line and adjuvant therapy from this checklist. FDA will review the checklist.

4. Please include information on the extent of study monitoring such as sites monitored, number of visits to each site during conduct of E3200, and the number of E3200 case report forms monitored at each site, by the NCI in the sBLA submission. Do the site monitor reports provide specific information on E3200? Can you provide information on the number of patients on E3200 that were audited?

   ECOG agreed to provide a brief overview. ECOG sites are audited every 36 months. The audit is based on the work of the entire institution of all the protocols they were involved in. NCI stated that they will discuss the extent of study monitoring on cooperative group trials at an upcoming meeting with the FDA.

5. In Table 2, you refer to 41 patients in the Expanded Patient Protocol. Please state whether this refers to patients enrolled by the CTSU. If not, please provide a copy of the Expanded Patient Protocol along with information on its relationship to E3200.

   NCI clarified that "EPP" means Expanded Participation Project. Patients on E3200 were enrolled directly from ECOG. Patients in the EPP were enrolled through the CTSU for other participating cooperative groups. The EPP involves practices which are not affiliated with the cooperative groups. Data from the EPP was submitted electronically and there were slight differences in the data collected from the EPP and the data collected from ECOG and CTSU. Genentech will submit data on these patients as well as an explanation of how these patients' data differs from standard ECOG data collected.

6. Please provide, in the sBLA, additional information on the data that was submitted to members of the Gastrointestinal Intergroup prior the final analysis of E3200 by the DMC.

   ECOG stated that the Gastrointestinal Intergroup made this request to the ECOG for planning purposes. The ECOG DMC reviewed the request and recommended that survival data as of 6-28-04 from arms A and B be provided to four people in the Gastrointestinal Intergroup. These four people signed confidentiality statements.

Issues Requiring Further Discussion:

Presentation of the integrated safety data for ——— Bevacizumab.

b(4)

Action Items for Genentech:

1. Provide a proposal for the integration of the ———————

2. Fax the ECOG eligibility checklist to Dr. Maher

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
Robert Justice, M.D.
Ellen Maher, M.D.

Office of Biostatistics
Biological Therapeutics Statistical Staff
Mark Rothmann, Ph.D.

Sponsor Attendees:
Genentech, Inc.
Alex Bajamonde, Ph.D., Director, Oncology Biostatistics
Lisa Bell, Ph.D., Manager, Regulatory Affairs
Julie Hambleton, M.D., Associate Director, Medical Affairs
Betty Nelson, M.A., Senior Biostatistican, Medical Affairs
Michelle Rohrer, Ph.D., Director, Regulatory Affairs
Somnath Sarkar
Jamey Skillings, M.D., Group Director, Medical Affairs
Kathleen Winson, Associate Operational Team Leader

ECOG
Robert Comis, M.D., Group Chair
Bruce Giantonio
Robert Gray, Ph.D., Group Statistician
Mary Steele

NCI
Meg Mooney, M.D., Senior Investigator, Clinical Investigations Branch, CTEP, DCTD

University of North Carolina
Richard Goldberg, M.D., Head, Colon Cancer Task Force for GI Intergroup