

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125085 / S-091

Trade Name: Avastin

Generic Name: Bevacizumab

Sponsor: Genentech, Inc.

Approval Date: February 22, 2008

Purpose: This supplement provides for a new indication:

For use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer

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BLA 125085 / S-091**

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APPLICATION NUMBER:
BLA 125085 / S-091

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125085/91

FEB 22 2008

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

Dear Dr. Rich:

Your request to supplement your biologics license application for bevacizumab to include a new indication for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer has been approved.

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

As requested in your letters of February 8 and 20, 2008, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies to further define the degree of clinical benefit to patients. You are required to conduct such studies with due diligence. As stated in 21 CFR 601.43(b), if you fail to meet these requirements, the Agency may, following a hearing, withdraw or modify approval.

Granting of this approval is contingent upon completion of clinical studies as outlined in your letters of February 8 and 20, 2008. This postmarketing study commitment is subject to the reporting requirements of 21 CFR 601.70:

1. To submit an efficacy supplement containing the final study reports (including summary analyses and primary datasets) and revised labeling based on the results from both of the following studies:
 - Study BO17708, "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Docetaxel in Comparison with Docetaxel Plus Placebo as First-Line Treatment for Patients with HER2-Negative Metastatic Breast Cancer." The protocol and a

revised statistical analysis plan were submitted to IND 7023 on January 8, 2008, and February 1, 2008, respectively. The study was completed on February 4, 2008.

- Study AVF3694g “A Multicenter, Phase 3, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer.” The protocol was submitted to IND 7023 on August 14, 2007. Patient accrual has been completed and the study will be completed by February 28, 2009. The supplement will be submitted by July 1, 2009.

We expect you to complete reporting of these studies within the framework described in your letter of February 20, 2008, and summarized above.

For administrative purposes, all submissions related to these postmarketing studies should be clearly designated “Subpart E Postmarketing Study Commitments.”

In addition, we note your following postmarketing commitments, specified in your letter of February 20, 2008, that are not a condition of the accelerated approval. These commitments are:

2. To submit a clinical study report, including summary analyses and primary datasets, for study AVF3693g, “A Phase 3, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Treated Metastatic Breast Cancer.” The protocol was submitted to IND 7023 on January 9, 2007. Patient accrual will be completed by June 30, 2009, and the study completed by March 31, 2010. The clinical study report will be submitted by January 31, 2011.
3. To submit a clinical study report, including summary analyses and datasets, for study BO20231, “A Randomized, Open-Label, 2-Arm, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Trastuzumab/Docetaxel Compared with Trastuzumab/Docetaxel Alone as First Line Treatment for Patients with HER2 Positive Locally Recurrent or Metastatic Cancer.” The protocol was submitted to IND 7023 on February 20, 2007. Patient accrual will be completed by July 31, 2011, and the study completed by April 30, 2012. The clinical study report will be submitted by April 1, 2013.
4. To submit a clinical study report, including summary analyses and datasets, for study CALGB 40503, “A Endocrine Therapy in Combination with Anti-VEGF Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Endocrine Therapy Alone or Endocrine Therapy plus Bevacizumab for Women with Hormone-Receptor Positive Advanced Breast Cancer.” The protocol was submitted to IND 7023 on January 19, 2007. Patient accrual will be completed by February 29, 2012, and the study completed by September 30, 2012. The clinical study report will be submitted by December 31, 2013.

Submit all study final reports to your BLA, STN BL 125085. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments

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

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

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

Within 21 days of the date of this letter, 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. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 125085/91." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

Marketing the product with final printed labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

As required by 21 CFR 601.45, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement with a cover letter requesting advisory comment. Send two copies of the promotional materials 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-

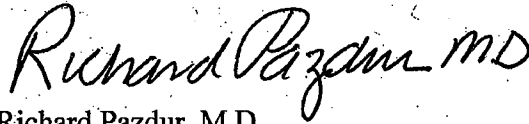
1266. Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

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 information regarding therapeutic biological products, including the addresses for submissions.

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

Sincerely,

A handwritten signature in black ink that reads "Richard Pazdur MD". The signature is written in a cursive style with a long, sweeping underline.

Richard Pazdur, M.D.

Director

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Enclosure: Revised Labeling

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APPLICATION NUMBER:
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OTHER ACTION LETTERS



Our STN: BL 125085/91

SEP 08 2006

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

Dear Dr. Garnick:

This letter is in regard to the supplement to your biologics license application for Bevacizumab for use in combination with taxane-based chemotherapy for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer, submitted under section 351 of the Public Health Service Act. We also refer to our July 7, 2006, electronic message and our July 21, 2006, letter.

We have completed the review of your supplement, including all amendments received through August 15, 2006. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

1. As indicated throughout the E2100 Clinical Study Report (CSR), ECOG continues to collect, enter and clean all study data, including patient information, safety, and efficacy data, following the December 30, 2005, data transfer to Genentech. Data submitted to support a license application must be locked, and data collection completed, cleaned up, and finalized. You must submit a complete clinical dataset as of a specified cut-off date; the selected cut-off date should be justified based on timing of the interim analysis resulting in public dissemination of study results. All data tables and line listings, including updated safety information should be updated for accuracy and completeness.
2. As indicated in our communications of July 7 and 21, 2006, the key efficacy endpoints of progression-free survival (PFS) and objective response rate analyses to support this sBLA were based on Genentech's review of ECOG's central review of investigator-reported tumor data from the E2100 study. Tumor data used by ECOG and Genentech consist solely of the investigator-reported tumor lesion measurements and comment fields. Given the subjective nature of the PFS endpoint, auditing to assess data integrity in a subset of the patients must be conducted. We have provided you with a list of 144 randomly selected patients for audit. Comments based on our review of the independent review committee (IRC) charter submitted on August 15, 2006, were forwarded to you on August 30, 2006, and were subsequently discussed on September 5, 2006. Depending on the findings from this evaluation, a more extensive audit may be required.

3. The E2100 CSR states that patients enrolled at non-ECOG sites (35%) had only limited data entered into the ECOG clinical database. It further states that because collection of these data was incomplete, these data were not used in the data analysis. We have serious concerns regarding the reliability and completeness of the clinical database. In order to verify the integrity of the data submitted to support licensure, please submit the eligibility checklist and a complete set of case report forms for all 722 patients enrolled in the E2100 study for review.
4. As indicated in our communications of July 7 and 21, 2006, the data to determine patient eligibility and adequacy of the conduct of E2100 trial are incomplete. Confirmation of eligibility by the ECOG central staff and as captured on the ECOG Eligibility Form is available in 605/722 patients (84%). ECOG case evaluation to determine protocol violation/deviation is available in only 261/722 patients (36%). This information is insufficient to determine if the trial supporting this sBLA was well conducted. Please provide the completed ECOG Eligibility forms and a complete dataset of case evaluation data for all 722 patients enrolled in the study. In addition, please provide the number of patients who were granted eligibility exceptions by treatment arm for all randomized patients as specified in the statistical analysis plan (SAP) of April 5, 2005. Such patients should be identifiable in the datasets by a specific flag denoting that patients did not meet pre-specified eligibility criteria.
5. Results of objective response presented in the CSR are based on a cutoff date of April 14, 2005. Based on Listing 16 2/4, a total of 188 patients (87 in the PAC arm and 101 in the PAC/BV arm) have an unevaluable or unknown best confirmed response because the data are still being cleaned up. You must submit a final and cleaned up dataset containing objective tumor response information. Objective tumor response information for all randomized patients, with measurable and non-measurable disease, must be provided.
6. Table 7, page 75 of the E2100 CSR indicates that 208/722 patients had no measurable disease at baseline (24.3% in the PC arm and 33.2% in the PC plus Bevacizumab arm). Please clarify how the information documenting non-measurable disease status was collected and provide further information on the site and extent of involvement for each lesion identified as having non-measurable disease. Additionally, PATE.xpt, indicates that “dismeas” is derived from baseline SLD. Please provide information (e.g., program) on how “dismeas” was derived.
7. Please confirm that the following information required in the protocol monitoring schema was not collected during the conduct of the study:
 - a. Medical and surgical histories.
 - b. Vital signs and physical findings.
 - c. Height and weight.

- d. ECOG performance status.
 - e. Clinical laboratory data.
 - f. Onset date of an adverse event (reporting period – i.e., 3-cycle durations, if event was observed more than once during a reporting period, the highest grade was reported).
 - g. Adverse events that led to treatment discontinuation if such events were rated as Grade 1 or 2 in severity.
 - h. Concomitant therapies were not collected in this study with the exception of Non-Protocol Therapy (NPT) received prior to tumor progression. Excluded therapies were not specified in the protocol, and NPT was not defined in the protocol.
 - i. The reason to initiate non-protocol treatment.
 - j. Information on therapy initiated following disease progression, including chemotherapy in either arm or any possible Bevacizumab use in the paclitaxel alone arm patients.
8. Summary results for all pre-specified analyses of the data, as described in the SAP, must be included in the clinical study report.
- a. Secondary endpoints include objective response rate and duration of objective response. As specified in the SAP, primary analysis for objective response rate would be performed using the intent to treat population and baseline measurable disease (yes, no) would be included as a stratification factor. Please submit results of objective response rate and duration of objective response rate for all randomized patients, as specified in the SAP, section 3.4.2.b and 3.4.2.c pages 853-854. Please provide a dataset to support your findings. Datasets should provide sufficient information to determine the cause of progression in patients with non-measurable disease and to confirm progression in patients with clinical rather than measurable progression.
 - b. Please provide the results of your analysis of data captured using quality of life (QoL) instruments to potentially assist in assessing the risk-benefit ratio.
 - c. Please submit the following exploratory analyses as specified in your SAP, section 3.4.3:
 - Overall survival and overall response rate analyses by baseline characteristics. The following demographic as baseline characteristics must be considered as specified in the SAP: disease-free interval (≤ 24 months, > 24 months), number of metastatic sites (< 3 , ≥ 3), adjuvant chemotherapy

(yes, no), ER status (ER positive, ER negative, ER unknown), ECOG performance status at study entry (0, ≥ 1), age (< 40, 40-65, > 65 years), race (white, non-white), baseline sum of the longest diameters of all target lesions, and HER2 expression status by immunohistochemistry.

9. The datasets provided do not contain sufficient information to determine how patients with unevaluable and unknown response status were evaluated regarding PFS. Please clarify how such patients were handled in the analysis of PFS.
10. Please provide a summary of the number of missing response assessments per time point as specified in the SAP of April 5, 2005.
11. Please provide comprehensive efficacy results based on the interim analysis, including patient disposition, results for secondary endpoints, i.e., Table 2, 10-14, 17 and figures 3-4 in the CSR. For each reported subgroup analysis please include event numbers as well as the hazard ratio.
12. Please provide a dataset as of the specified data cut-off date (as discussed in comment 1) including all the variables in the current PATE.xpt data.
13. Please provide SAS programs used for the derivation of Genentech's PFS and response outcome, i.e., variables pdfdt7, pfscen7, pdfdt8b, pfstime7, pftime8b, pfcen8b, pdiadt7, pdia7, crspi7, crprdt7, trtpdif7, pftype8b, and pfstype7 in TUMORPAT.xpt.
14. There is insufficient and incomplete information to permit a valid assessment of the toxicity profile of Bevacizumab in combination with paclitaxel. As stated in comment 1 above, the safety data of E2100 is incomplete, as ECOG and Genentech continue to collect, enter and clean up pre-existing data at the time of your sBLA submission. You must submit a complete, cleaned up dataset for review. All tables and line listings must be updated. Concerning the submitted information, we have the following comments and requests:
 - a. There is insufficient information to evaluate the extent of drug exposure in the E2100 study. In addition to number of cycles and number of doses received, please provide the cumulative dose (mg/m² or mg/kg), dose intensity (mg/m²/cycle or mg/kg/cycle), number of dose modifications, and number and length of dose delays/omissions for each arm and for each agent, i.e. regarding both Bevacizumab and paclitaxel dosing in the combination arm. The same information should also be provided for each agent separately. Please refer to the "Guidance for Industry – Cancer Drug and Biological Products – Clinical Data and Marketing Applications" at <http://www.fda.gov/cder/guidance/4332fn1.pdf> and to the SAP of April 5, 2005. Please provide data in individual line listings and in tabular format. Please provide a SAS dataset.
 - b. Regarding the dose modification/omission, 219 patients (63.7%) in the paclitaxel arm and 313 (87.4%) in the paclitaxel/Bevacizumab arm had a dose modification

or omission. Please provide the line listing and in tabular format, the reason, either planned or unplanned, that lead to dose modification/omission of paclitaxel, Bevacizumab, or paclitaxel and Bevacizumab. Please refer to the “Guidance for Industry – Cancer Drug and Biological Products – Clinical Data and Marketing Applications” at <http://www.fda.gov/cder/guidance/4332fnl.pdf> and to the SAP of April 5, 2005.

- c. For the paclitaxel/Bevacizumab arm, please identify the patients who discontinued Bevacizumab and continued on paclitaxel alone and patients who discontinued paclitaxel and continued Bevacizumab alone prior to disease progression.
- d. Listing 16.2/13 provides deaths and study discontinuation due to toxicity of patients treated in the paclitaxel alone arm. Please provide a similar listing for the paclitaxel and Bevacizumab arm.
- e. Listing 16.2/12 provides adverse events that occurred in temporal proximity to protocol therapy discontinuation. Please provide in a tabular format for the paclitaxel and paclitaxel plus Bevacizumab arm, the causes of adverse events leading to (reported in temporal proximity) treatment discontinuation.
- f. Adverse events reported to NCI AdEERS for the paclitaxel arm were submitted to CTEP, but not provided to Genentech. These reports were sent to MedWatch. Please provide copies of the MedWatch reports related to E2100 study.
- g. Please provide a single adverse event dataset that includes all sources of adverse event collection including the E2100 toxicity form, AdEERS, Off Study Forms and MedWatch Reports. Please design the dataset so that the collection source is identified and searchable.
- h. The case narratives provided in the sBLA are frequently incomplete and with discrepancies that do not allow a full understanding of the clinical picture. Following are two examples of incomplete and inconsistent patient narratives:
 - 1) Patient No. 26004: narrative describes a 66 year-old female patient who died from a cause other than progressive disease more than 30 days after the last dose of protocol therapy that was possibly related to Bevacizumab. The narrative states that “the patient was randomized on 11 July, 2003... sites of disease involvement include bone... The date of the first protocol therapy administration was 17 July 2003. Between 8 January 2004 and 31 March 2004 (cycles 7-9), she experienced grade 3 sensory neuropathy. Data capture in the AdEERS database indicated that the patient experienced grade 3 abdominal pain, diarrhea with black tarry stools on 4 May, 2004. The patient’s last dose of bevacizumab prior to the events was administered on 28 April 2004 (cycle 9)... The patient received treatment with paclitaxel only on 27 May 2004. On 27 May, 2004 she became

hypotensive and bradycardic... pronounced death on _____” The next paragraph of the narrative states: “... The last date of protocol therapy administration was reported as 18 March 2004. The last cycle of bevacizumab (Cycle 9) was reported as 4 March 2004...”

b(6)

- 2) Patient No. 21407: narrative describes a 44 year-old patient with an event reported through AdEERS. The narrative states that “the patient was randomized on 19 March 2004. Sites of disease involvement included the right gluteous. The date of first protocol therapy was March 22, 2004. The patient was seen in office for cycle 2 with fatigue and low blood counts. She received paclitaxel and bevacizumab and was admitted for pain control, anemia and lower extremity edema. She was discharged on _____ and died on _____. The date of disease progression was 29 April 2004.” The narrative further states that the patient had “Grade 5 constitutional symptoms (disease progression), Grade 4 increased bilirubin, Grade 4 bone pain, a Grade 3 GI bleeding event, Grade 3 increased prothrombin time, a Grade 3 hypoxia were reported.” This narrative is incomplete as it does not provide sufficient information regarding the patient’s clinical picture. The cause of the Grade 4 bilirubin, the cause, time of onset and resolution of GI bleeding or the clinical or radiological evidence to support disease progression are unclear.

b(6)

Genentech must review and revise all case narratives accordingly. Narratives must be complete and contain the pertinent information necessary to make clinical sense. All reporting discrepancies between the CRF and AdEERS must be queried and solved by Genentech. We acknowledge receipt of your electronic mail of August 31, 2006, proposing revisions to the case narrative format and content.

- i. To facilitate and expedite review, please provide in a tabular format, a list of all patients with narratives, with hyperlinks, page no. and the reason for the narrative reporting.

Patient ID	Hyperlink	Reason for Narrative Reporting	Page No.

15. Regarding financial disclosure:

- a. Please provide signed financial disclosure statements for the following ECOG study administrative body:
 - 1) Study Chairperson: Kathy D. Miller, MD
 - 2) Study Co-Chairperson: Robin Zon, MD

- 3) Pathology Co-Chairperson: Ann Thor, MD
- 4) Statistician: Molin Wang, Ph.D.
- 5) QOL Sub-Committee Chairperson: David Cella
- 6) Breast Committee Chairperson: George W. Sledge Jr., MD
- 7) Correlative Co-Chairperson: Kathy D. Miller, MD
- 8) Community Co-Chairperson: Thomas Shaphner, MD
- 9) NCCTG Co-Chairperson: Edith Perez, MD
- 10) NCIC CTG Co-Chairperson: Tamar Shenkier, MD
- 11) NSABP Co-Chairperson: Melody Cobleigh, MD

We note that Dr. Kathy Miller (Study Chairperson) failed to reply to the Financial Disclosure Information requests (requests sent on 11/11/05 and 12/15/05).

- b. Please provide the name/affiliation of the members of the ECOG Data Monitoring Committee (DMC) involved in E2100 data analysis. Please provide signed financial disclosure statements for the DMC members.
16. Section 6, page 20 of the E2100 CSR states that data management was conducted in accordance with ECOG Policy and Standard Procedures Manual, Version 4 (Nov 2000) and Version 5 (March 2003). Please provide the ECOG Policy and Standard Procedures Manual.
 17. Section 6, page 20, and section 16.1.8, page 835 of the E2100 CSR states that each cooperative group conducted audits of its participating sites using policies and procedures modeled after guidance documents. Please provide audit documentation from all cooperative groups for the investigational sites involved in E2100 study.
 18. Please note that the data contained in your submission does not support a broad labeling claim for use of Bevacizumab in combination with the drug class taxane-based chemotherapy. You will need to conduct an additional study(ies) to establish the clinical effectiveness of Bevacizumab in combination with other taxanes alone and in combination with other chemotherapies.

We reserve comment on the proposed labeling until the supplement is otherwise acceptable.

You may request a meeting or teleconference with CDER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as

described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products – February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the supplement; (2) notify us of your intent to file an amendment; (3) withdraw the supplement; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the supplement. In the absence of any of the above responses, we may initiate action to deny the supplement.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

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, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 796-2320.

Sincerely,



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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125085 / S-091

LABELING

1 **1.14.1.3 Draft Labeling Text**2 **AVASTIN®**
3 **(Bevacizumab)**4 **For Intravenous Use**5 **WARNINGS**6 **Gastrointestinal Perforations**

7 AVASTIN administration can result in the development of gastrointestinal
8 perforation, in some instances resulting in fatality. Gastrointestinal
9 perforation, sometimes associated with intra-abdominal abscess, occurred
10 throughout treatment with AVASTIN (i.e., was not correlated to duration
11 of exposure). The incidence of gastrointestinal perforation
12 (gastrointestinal perforation, fistula formation, and/or intra-abdominal
13 abscess) in patients with colorectal cancer and in patients with non-small
14 cell lung cancer (NSCLC) receiving AVASTIN was 2.4% and 0.9%,
15 respectively. The typical presentation was reported as abdominal pain
16 associated with symptoms such as constipation and vomiting.

17 Gastrointestinal perforation should be included in the differential
18 diagnosis of patients presenting with abdominal pain on AVASTIN.

19 AVASTIN therapy should be permanently discontinued in patients with
20 gastrointestinal perforation. (See WARNINGS:

21 **Gastrointestinal Perforations and DOSAGE AND**
22 **ADMINISTRATION: Dose Modifications.)**

23 **Wound Healing Complications**

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

32 Hemorrhage

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

41 DESCRIPTION

42 AVASTIN[®] (Bevacizumab) is a recombinant humanized monoclonal
43 IgG1 antibody that binds to and inhibits the biologic activity of human
44 vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay
45 systems. Bevacizumab contains human framework regions and the
46 complementarity-determining regions of a murine antibody that binds to
47 VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary
48 mammalian cell expression system in a nutrient medium containing the
49 antibiotic gentamicin and has a molecular weight of approximately
50 149 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to
51 pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion.
52 AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use
53 vials to deliver 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg
54 product is formulated in 240 mg α, α -trehalose dihydrate, 23.2 mg sodium
55 phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic,
56 anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The
57 400 mg product is formulated in 960 mg α, α -trehalose dihydrate, 92.8 mg
58 sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate
59 (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection,
60 USP.

61 CLINICAL PHARMACOLOGY**62 Mechanism of Action**

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

70 Pharmacokinetics

71 The pharmacokinetic profile of Bevacizumab was assessed using an assay
72 that measures total serum Bevacizumab concentrations (i.e., the assay did
73 not distinguish between free Bevacizumab and Bevacizumab bound to
74 VEGF ligand). Based on a population pharmacokinetic analysis of
75 491 patients who received 1 to 20 mg/kg of AVASTIN weekly, every
76 2 weeks, or every 3 weeks, the estimated half-life of Bevacizumab was
77 approximately 20 days (range 11–50 days). The predicted time to reach
78 steady state was 100 days. The accumulation ratio following a dose of
79 10 mg/kg of Bevacizumab every 2 weeks was 2.8.

80 The clearance of Bevacizumab varied by body weight, by gender, and by
81 tumor burden. After correcting for body weight, males had a higher
82 Bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger V_c
83 (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or
84 above median value of tumor surface area) had a higher Bevacizumab
85 clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens
86 below the median. In a randomized study of 813 patients (Study 1), there
87 was no evidence of lesser efficacy (hazard ratio for overall survival) in
88 males or patients with higher tumor burden treated with AVASTIN as
89 compared to females and patients with low tumor burden. The
90 relationship between Bevacizumab exposure and clinical outcomes has not
91 been explored.

92 Special Populations

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

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

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

101 CLINICAL STUDIES**102 AVASTIN[®] In Metastatic Colorectal Cancer (mCRC)**

103 The safety and efficacy of AVASTIN in the treatment of patients with
104 metastatic carcinoma of the colon or rectum were studied in three
105 randomized, controlled clinical trials in combination with intravenous
106 5-fluorouracil-based chemotherapy. The activity of AVASTIN in patients
107 with metastatic colorectal cancer that progressed on or after receiving both
108 irinotecan based- and oxaliplatin based-chemotherapy regimens was
109 evaluated in an open-access trial in combination with intravenous
110 5-fluorouracil-based chemotherapy.

111 AVASTIN in Combination with Bolus-IFL

112 Study 1 was a randomized, double-blind, active-controlled clinical trial
113 evaluating AVASTIN as first-line treatment of metastatic carcinoma of the
114 colon or rectum. Patients were randomized to bolus-IFL (irinotecan
115 125 mg/m² IV, 5-fluorouracil 500 mg/m² IV, and leucovorin 20 mg/m² IV
116 given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1),
117 bolus-IFL plus AVASTIN (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV
118 plus AVASTIN (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3
119 was discontinued, as pre-specified, when the toxicity of AVASTIN in
120 combination with the bolus-IFL regimen was deemed acceptable.

121 Of the 813 patients randomized to Arms 1 and 2, the median age was 60,
 122 40% were female, and 79% were Caucasian. Fifty-seven percent had an
 123 ECOG performance status of 0. Twenty-one percent had a rectal primary
 124 and 28% received prior adjuvant chemotherapy. In the majority of
 125 patients, 56%, the dominant site of disease was extra-abdominal, while the
 126 liver was the dominant site in 38% of patients. Results are presented in
 127 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
<u>Overall Survival^a</u>		
Median (months)	15.6	20.3
Hazard ratio		0.66
<u>Progression-free Survival^a</u>		
Median (months)	6.2	10.6
Hazard ratio		0.54
<u>Overall Response Rate^b</u>		
Rate (percent)	35%	45%
<u>Duration of Response</u>		
Median (months)	7.1	10.4

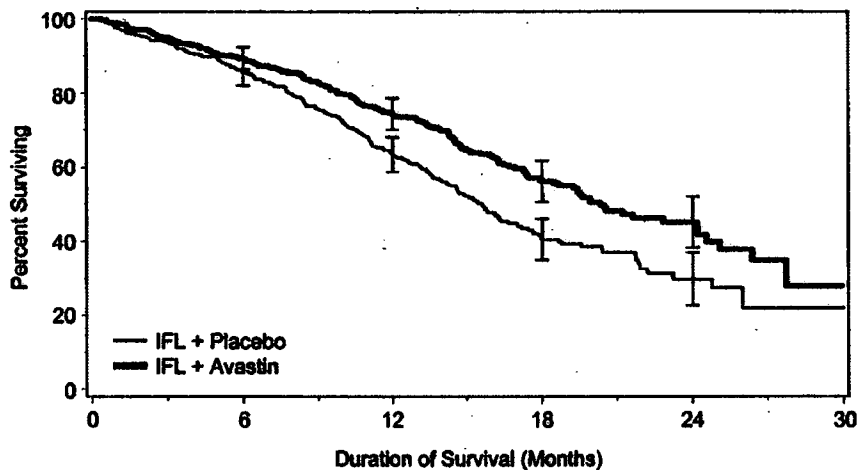
^ap<0.001 by stratified logrank test.

^bp<0.01 by χ^2 test.

128

129
130

Figure 1
Duration of Survival in Study 1



131

132 Error bars represent 95% confidence intervals.

133

134 The clinical benefit of AVASTIN, as measured by survival in the two
135 principal arms, was seen in the subgroups defined by age (<65 yrs,
136 ≥65 yrs) and gender.

137 Among the 110 patients enrolled in Arm 3, median overall survival was
138 18.3 months, median progression-free survival was 8.8 months, overall
139 response rate was 39%, and median duration of response was 8.5 months.

140 **AVASTIN in Combination with 5-FU/LV Chemotherapy**

141 Study 2 was a randomized, active-controlled clinical trial testing
142 AVASTIN in combination with 5-FU/LV as first-line treatment of
143 metastatic colorectal cancer. Patients were randomized to receive
144 5-FU/LV (5-fluorouracil 500 mg/m², leucovorin 500 mg/m² weekly for
145 6 weeks every 8 weeks) or 5-FU/LV plus AVASTIN (5 mg/kg every
146 2 weeks) or 5-FU/LV plus AVASTIN (10 mg/kg every 2 weeks).
147 The primary endpoints of the trial were objective response rate and
148 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

149

150 Progression-free survival was significantly longer in patients receiving
 151 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not
 152 receiving AVASTIN. However, overall survival and overall response rate
 153 were not significantly different. Outcomes for patients receiving 5-FU/LV
 154 plus AVASTIN at 10 mg/kg were not significantly different than for
 155 patients who did not receive AVASTIN.

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

158 Study 3 was an open-label, randomized, 3-arm, active-controlled,
 159 multicenter clinical trial evaluating AVASTIN alone, AVASTIN in
 160 combination with 5-FU/LV and oxaliplatin (FOLFOX4), and FOLFOX4
 161 alone in the second-line treatment of metastatic carcinoma of the colon or
 162 rectum. Patients were previously treated with irinotecan and 5-FU for
 163 initial therapy for metastatic disease or as adjuvant therapy. Patients were
 164 randomized to FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and leucovorin
 165 200 mg/m² concurrently IV, then 5-FU 400 mg/m² IV bolus followed by
 166 600 mg/m² continuously IV; Day 2: leucovorin 200 mg/m² IV, then 5-FU
 167 400 mg/m² IV bolus followed by 600 mg/m² continuously IV; repeated
 168 every 2 weeks), FOLFOX4 plus AVASTIN, or AVASTIN monotherapy.
 169 AVASTIN was administered at a dose of 10 mg/kg every 2 weeks and for

170 patients in the FOLFOX4 plus AVASTIN arm, prior to the FOLFOX4
171 chemotherapy on Day 1.

172 Of the 829 patients randomized to the three arms, the median age was
173 61 years, 40% were female, 87% were Caucasian, and 49% had an ECOG
174 performance status of 0. Twenty-six percent had received prior radiation
175 therapy, and 80% received prior adjuvant chemotherapy. Ninety-nine
176 percent received prior irinotecan, with or without 5-FU for metastatic
177 colorectal cancer, and 1% received prior irinotecan and 5-FU as adjuvant
178 therapy.

179 The AVASTIN monotherapy arm of Study 3 was closed to accrual after
180 enrollment of 244 of the planned 290 patients following a planned interim
181 analysis by the data monitoring committee (DMC), based on evidence of
182 decreased survival in the AVASTIN alone arm as compared to the
183 FOLFOX4 alone arm. In the two remaining study arms, overall survival
184 (OS) was significantly longer in patients receiving AVASTIN in
185 combination with FOLFOX4 as compared to those receiving FOLFOX4
186 alone (median OS 13.0 mos vs. 10.8 mos; hazard ratio 0.75 [95% CI 0.63,
187 0.89], $p=0.001$ stratified log rank test). In addition, patients treated with
188 AVASTIN in combination with FOLFOX4 were reported to have
189 significantly longer progression-free survival and a higher overall
190 response rate based on investigator assessment. The clinical benefit of
191 AVASTIN, as measured by survival, was seen in the subgroups defined by
192 age (<65 yrs, ≥ 65 yrs) and gender.

193 **AVASTIN in Third-Line Metastatic Colorectal Cancer**

194 Study 4 was an open access, multicenter, single arm study that evaluated
195 the activity of AVASTIN in combination with bolus or infusional
196 5-FU/LV in 339 patients with metastatic colorectal cancer with disease
197 progression following both irinotecan- and oxaliplatin-containing
198 chemotherapy regimens. The majority (73%) of patients received
199 concurrent 5-FU/LV according to a bolus regimen.

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

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

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

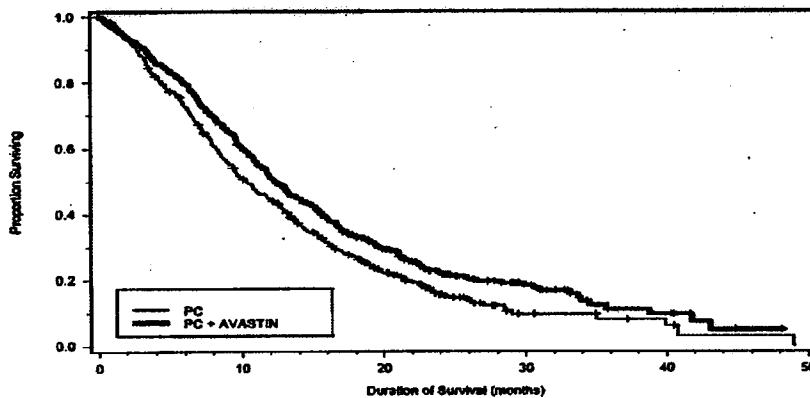
209 In Study 5, chemotherapy-naïve patients with locally advanced, metastatic
210 or recurrent non-squamous NSCLC were randomized (1:1) to receive six
211 cycles of paclitaxel 200 mg/m² and carboplatin AUC=6.0, both by IV
212 infusion on day 1 (PC) or PC in combination with AVASTIN at a dose of
213 15 mg/kg by IV infusion on day 1 (PC plus AVASTIN). After completion
214 or upon discontinuation of chemotherapy, patients in the PC plus
215 AVASTIN arm continued to receive AVASTIN alone until disease
216 progression or until unacceptable toxicity. Cycles were repeated every
217 21 days. Patients with predominant squamous histology (mixed cell type
218 tumors only), central nervous system (CNS) metastasis, gross hemoptysis
219 (≥1/2 tsp of red blood), or unstable angina and those receiving therapeutic
220 anticoagulation were excluded. The main outcome measure of the study
221 was duration of survival.

222 Among the 878 patients randomized to the two treatment arms, the median
223 age was 63, 46% were female, 43% were ≥age 65, and 28% had ≥5%
224 weight loss at study entry. Eleven percent had recurrent disease and of the
225 remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with
226 malignant pleural effusion and 76% had Stage IV disease. The survival
227 curves are presented in Figure 2. Overall survival was statistically
228 significantly higher among patients receiving PC plus AVASTIN
229 compared with those receiving PC alone; median OS was 12.3 mos vs.
230 10.3 mos (hazard ratio 0.80 [repeated 95% CI 0.68, 0.94], final p-value

231 0.013, stratified log-rank test). Based on investigator assessment which
 232 was not independently verified, patients were reported to have longer
 233 progression-free survival with AVASTIN in combination with PC
 234 compared to PC alone.

235
 236

Figure 2
 Duration of Survival in Study 5



237
 238

239 In an exploratory analyses across patient subgroups, the impact of
 240 AVASTIN on overall survival was less robust in the following: women
 241 [HR=0.99 (95% CI: 0.79, 1.25)], age \geq 65 years [HR=0.91 (95% CI:
 242 0.72, 1.14)] and patients with \geq 5% weight loss at study entry [HR=0.96
 243 (95% CI: 0.73, 1.26)].

244 INDICATIONS AND USAGE

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

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

251 CONTRAINDICATIONS

252 None.

253 WARNINGS**254 Gastrointestinal Perforations (See DOSAGE AND
255 ADMINISTRATION: Dose Modifications)**

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

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

277 Permanently discontinue AVASTIN in patients with gastrointestinal
278 perforation (gastrointestinal perforation, fistula formation, and/or
279 intra-abdominal abscess).

280 **Non-Gastrointestinal Fistula Formation (See DOSAGE AND**
281 **ADMINISTRATION: Dose Modifications)**

282 Non-gastrointestinal fistula formation has been reported in patients treated
283 with AVASTIN in controlled clinical studies (with an incidence of
284 < 0.3%) and in post-marketing experience, in some cases with fatal
285 outcome. Fistula formation involving the following areas of the body
286 other than the gastrointestinal tract have been reported:
287 tracheo-esophageal, bronchopleural, biliary, vagina and bladder. Events
288 were reported throughout treatment with Avastin, with most events
289 occurring within the first 6 months.

290 Permanently discontinue AVASTIN in patients with fistula formation
291 involving an internal organ.

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

294 AVASTIN impairs wound healing in animal models. In clinical studies of
295 AVASTIN, patients were not allowed to receive AVASTIN until at least
296 28 days had elapsed following surgery. In clinical studies of AVASTIN in
297 combination with chemotherapy, there were 6 instances of dehiscence
298 among 788 patients (0.8%).

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

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

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

314 **Hemorrhage (See DOSAGE AND ADMINISTRATION:**
315 **Dose Modifications)**

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

320 In Study 6, four of 13 (31%) AVASTIN-treated patients with squamous
321 cell histology and two of 53 (4%) AVASTIN-treated patients with
322 histology other than squamous cell, experienced serious or fatal
323 pulmonary hemorrhage as compared to none of the 32 (0%) patients
324 receiving chemotherapy alone. Of the patients experiencing pulmonary
325 hemorrhage requiring medical intervention, many had cavitation and/or
326 necrosis of the tumor, either pre-existing or developing during AVASTIN
327 therapy. In Study 5, the rate of pulmonary hemorrhage requiring medical
328 intervention for the PC plus AVASTIN arm was 2.3% (10 of 427)
329 compared to 0.5% (2 of 441) for the PC alone arm. There were seven
330 deaths due to pulmonary hemorrhage reported by investigators in the PC
331 plus AVASTIN arm as compared to one in the PC alone arm. Generally,
332 these serious hemorrhagic events presented as major or massive
333 hemoptysis without an antecedent history of minor hemoptysis during
334 Avastin therapy. Do not administer AVASTIN to patients with recent
335 history of hemoptysis of $\geq 1/2$ tsp of red blood. Other serious bleeding
336 events occurring in patients receiving AVASTIN across all indications
337 include gastrointestinal hemorrhage, subarachnoid hemorrhage, and
338 hemorrhagic stroke. Some of these events were fatal. (See ADVERSE
339 REACTIONS: Hemorrhage.)

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

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

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

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

357 In a pooled analysis of randomized, controlled clinical trials involving
358 1745 patients, the incidence of ATE was 4.4% among patients treated with
359 AVASTIN in combination with chemotherapy and 1.9% among patients
360 receiving chemotherapy alone. Fatal outcomes for these events occurred
361 in 7 of 963 patients (0.7%) who were treated with AVASTIN in
362 combination with chemotherapy, compared to 3 of 782 patients (0.4%)
363 who were treated with chemotherapy alone. The incidences of both
364 cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial
365 events (2.1% vs. 1.0%) were increased in patients receiving AVASTIN
366 compared to chemotherapy alone. The relative risk of ATE was greater in
367 patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65
368 (2.1% vs. 1.4%). (See **PRECAUTIONS: Geriatric Use.**)

369 The safety of resumption of AVASTIN therapy after resolution of an ATE
370 has not been studied. Permanently discontinue AVASTIN in patients who

371 experience a severe ATE during treatment. (See **DOSAGE AND**
372 **ADMINISTRATION: Dose Modifications and PRECAUTIONS:**
373 **Geriatric Use.**)

374 **Hypertension (See DOSAGE AND ADMINISTRATION:**
375 **Dose Modifications)**

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

379 Medication classes used for management of patients with NCI-CTC
380 Grade 3 hypertension receiving AVASTIN included
381 angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and
382 calcium channel blockers. Development or worsening of hypertension can
383 require hospitalization or require discontinuation of AVASTIN in up to
384 1.7% of patients. Hypertension can persist after discontinuation of
385 AVASTIN. Complications can include hypertensive encephalopathy
386 (in some cases fatal) and CNS hemorrhage.

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

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

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

397 RPLS has been reported in clinical studies (with an incidence of <0.1%)
398 and in post-marketing experience. RPLS is a neurological disorder which
399 can present with headache, seizure, lethargy, confusion, blindness and
400 other visual and neurologic disturbances. Mild to severe hypertension

401 may be present, but is not necessary for diagnosis of RPLS. Magnetic
402 Resonance Imaging (MRI) is necessary to confirm the diagnosis of RPLS.
403 The onset of symptoms has been reported to occur from 16 hours to 1 year
404 after initiation of AVASTIN.

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

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

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

417 **Proteinuria (See DOSAGE AND ADMINISTRATION:**
418 **Dose Modifications)**

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

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

428 The highest incidence of proteinuria was observed in a dose-ranging,
429 placebo-controlled, randomized study of AVASTIN in patients with
430 metastatic renal cell carcinoma, an indication for which AVASTIN is not

431 approved, 24-hour urine collections were obtained in approximately half
432 the patients enrolled. Among patients in whom 24-hour urine collections
433 were obtained, four of 19 (21%) patients receiving AVASTIN at 10 mg/kg
434 every two weeks, two of 14 (14%) patients receiving AVASTIN at
435 3 mg/kg every two weeks, and none of the 15 placebo patients
436 experienced NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

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

445 **Congestive Heart Failure**

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

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

460 PRECAUTIONS**461 General**

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

464 Infusion Reactions

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

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

477 Surgery

478 AVASTIN therapy should not be initiated for at least 28 days following
479 major surgery. The surgical incision should be fully healed prior to
480 initiation of AVASTIN. Because of the potential for impaired wound
481 healing, AVASTIN should be suspended prior to elective surgery.
482 The appropriate interval between the last dose of AVASTIN and elective
483 surgery is unknown; however, the half-life of AVASTIN is estimated to be
484 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and
485 the interval chosen should take into consideration the half-life of the drug.
486 (See **WARNINGS: Gastrointestinal Perforations and**
487 **Wound Healing Complications.**)

488 Cardiovascular Disease

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

498 Laboratory Tests

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

505 Patients receiving AVASTIN should be monitored for the development or
506 worsening of proteinuria with serial urinalyses. Patients with a 2+ or
507 greater urine dipstick reading should undergo further assessment, e.g., a
508 24-hour urine collection. (See **WARNINGS: Proteinuria and DOSAGE
509 AND ADMINISTRATION: Dose Modifications.**)

510 Drug Interactions

511 No formal drug interaction studies with anti-neoplastic agents have been
512 conducted. In Study 1, patients with colorectal cancer were given
513 irinotecan/5-FU/leucovorin (bolus-IFL) with or without AVASTIN.
514 Irinotecan concentrations were similar in patients receiving bolus-IFL
515 alone and in combination with AVASTIN. The concentrations of SN38,
516 the active metabolite of irinotecan, were on average 33% higher in patients
517 receiving bolus-IFL in combination with AVASTIN when compared with
518 bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus AVASTIN

519 had a higher incidence of NCI-CTC Grade 3–4 diarrhea and neutropenia.
520 Due to high inter-patient variability and limited sampling, the extent of the
521 increase in SN38 levels in patients receiving concurrent irinotecan and
522 AVASTIN is uncertain.

523 In Study 6, based on limited data, there did not appear to be a difference in
524 the mean exposure of either carboplatin or paclitaxel when each was
525 administered alone or in combination with AVASTIN. However, 3 of the
526 8 patients receiving AVASTIN plus paclitaxel/carboplatin had
527 substantially lower paclitaxel exposure after four cycles of treatment (at
528 Day 63) than those at Day 0, while patients receiving
529 paclitaxel/carboplatin without AVASTIN had a greater paclitaxel
530 exposure at Day 63 than at Day 0.

531 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

547 Pregnancy Category C

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

554 Angiogenesis is critical to fetal development and the inhibition of
555 angiogenesis following administration of AVASTIN is likely to result in
556 adverse effects on pregnancy. There are no adequate and well-controlled
557 studies in pregnant women. AVASTIN should be used during pregnancy
558 or in any woman not employing adequate contraception only if the
559 potential benefit justifies the potential risk to the fetus. All patients should
560 be counseled regarding the potential risk of AVASTIN to the developing
561 fetus prior to initiation of therapy. If the patient becomes pregnant while
562 receiving AVASTIN, she should be apprised of the potential hazard to the
563 fetus and/or the potential risk of loss of pregnancy. Patients who
564 discontinue AVASTIN should also be counseled concerning the prolonged
565 exposure following discontinuation of therapy (half-life of approximately
566 20 days) and the possible effects of AVASTIN on fetal development.

567 Nursing Mothers

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

575 Pediatric Use

576 The safety and effectiveness of AVASTIN in pediatric patients has not
577 been studied. However, physal dysplasia was observed in juvenile

578 cynomolgus monkeys with open growth plates treated for four weeks with
579 doses that were less than the recommended human dose based on mg/kg
580 and exposure. The incidence and severity of physal dysplasia were
581 dose-related and were at least partially reversible upon cessation of
582 treatment.

583 **Geriatric Use**

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

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

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

606 Of the 742 patients enrolled in Genentech-sponsored clinical studies in
607 which all adverse events were captured, 212 (29%) were age 65 or older

608 and 43 (6%) were age 75 or older. Adverse events of any severity that
609 occurred at a higher incidence in the elderly as compared to younger
610 patients, in addition to those described above, were dyspepsia,
611 gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice
612 alteration.

613 In an exploratory, pooled analysis of 1745 patients treated in
614 five randomized, controlled studies, there were 618 (35%) patients age
615 65 or older and 1127 patients less than 65 years of age. The overall
616 incidence of arterial thromboembolic events was increased in all patients
617 receiving AVASTIN with chemotherapy as compared to those receiving
618 chemotherapy alone, regardless of age. However, the increase in arterial
619 thromboembolic events incidence was greater in patients 65 and over
620 (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).
621 (See **WARNINGS: Arterial Thromboembolic Events.**)

622 **ADVERSE REACTIONS**

623 The most serious adverse reactions in patients receiving AVASTIN were:

- 624 • Gastrointestinal Perforations (see **WARNINGS**)
- 625 • Non-Gastrointestinal Fistula Formation (see **WARNINGS**)
- 626 • Wound Healing Complications (see **WARNINGS**)
- 627 • Hemorrhage (see **WARNINGS**)
- 628 • Arterial Thromboembolic Events (see **WARNINGS**)
- 629 • Hypertensive Crises (see **WARNINGS: Hypertension**)
- 630 • Reversible Posterior Leukoencephalopathy Syndrome
631 (see **WARNINGS**)
- 632 • Neutropenia and Infection (see **WARNINGS**)
- 633 • Nephrotic Syndrome (see **WARNINGS: Proteinuria**)
- 634 • Congestive Heart Failure (see **WARNINGS**)

635 The most common adverse events in patients receiving AVASTIN were
636 asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea,

637 vomiting, anorexia, stomatitis, constipation, upper respiratory infection,
638 epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

639 **Adverse Reactions in Clinical Trials**

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

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

651 **Gastrointestinal Perforation**

652 The incidence of gastrointestinal perforation across all studies ranged from
653 0–3.7%. The incidence of gastrointestinal perforation, in some cases fatal,
654 in patients with mCRC receiving AVASTIN alone or in combination with
655 chemotherapy was 2.4% compared to 0.3% in patients receiving only
656 chemotherapy. The incidence of gastrointestinal perforation in NSCLC
657 patients receiving AVASTIN was 0.9% compared to 0% in patients
658 receiving only chemotherapy. (See WARNINGS:

659 **Gastrointestinal Perforations and DOSAGE AND**
660 **ADMINISTRATION: Dose Modifications.)**

661 **Non-Gastrointestinal Fistula Formation**

662 (See WARNINGS: **Non-Gastrointestinal Fistula Formation,**
663 **DOSAGE AND ADMINISTRATION: Dose Modifications.)**

664 Wound Healing Complications

665 The incidence of post-operative wound healing and/or bleeding
666 complications was increased in patients with mCRC receiving AVASTIN
667 as compared to patients receiving only chemotherapy. Among patients
668 requiring surgery on or within 60 days of receiving study treatment,
669 wound healing and/or bleeding complications occurred in 15% (6/39) of
670 patients receiving bolus-IFL plus AVASTIN as compared to 4% (1/25) of
671 patients who received bolus-IFL alone. In the same study, the incidence
672 of wound dehiscence was also higher in the AVASTIN-treated patients
673 (1% vs. 0.5%).

674 Hemorrhage

675 Severe or fatal hemorrhages, including hemoptysis, gastrointestinal
676 bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding
677 occurred up to five-fold more frequently in AVASTIN treated patients
678 compared to patients treated with chemotherapy alone. NCI-CTC
679 Grade 3–5 hemorrhagic events occurred in 4.7% of NSCLC patients and
680 5.2% of mCRC patients receiving AVASTIN compared to 1.1% and 0.7%
681 for the control groups respectively. (See **WARNINGS: Hemorrhage.**)

682 The incidence of epistaxis was higher (35% vs. 10%) in patients with
683 mCRC receiving bolus-IFL plus AVASTIN compared with patients
684 receiving bolus-IFL plus placebo. These events were generally mild in
685 severity (NCI-CTC Grade 1) and resolved without medical intervention.
686 Additional mild to moderate hemorrhagic events reported more frequently
687 in patients receiving bolus-IFL plus AVASTIN when compared to those
688 receiving bolus-IFL plus placebo included gastrointestinal hemorrhage
689 (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage
690 (4% vs. 2%). (See **WARNINGS: Hemorrhage and DOSAGE AND**
691 **ADMINISTRATION: Dose Modifications.**)

692 Arterial Thromboembolic Events

693 The incidence of arterial thromboembolic events was increased in NSCLC
694 patients receiving PC plus AVASTIN (3.0%) compared with patients

695 receiving PC alone (1.4%). Five events were fatal in the PC plus
696 AVASTIN arm, compared with 1 event in the PC alone arm. This
697 increased risk is consistent with that observed in patients with mCRC.
698 (See **WARNINGS: Arterial Thromboembolic Events, DOSAGE AND**
699 **ADMINISTRATION: Dose Modifications, and PRECAUTIONS:**
700 **Geriatric Use.**)

701 Venous Thromboembolic Events

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

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

722 Hypertension

723 Fatal CNS hemorrhage complicating AVASTIN induced hypertension can
724 occur.

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

Table 3
Incidence of Hypertension and Severe Hypertension in Study 1

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

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

728

729 Among patients with severe hypertension in the AVASTIN arms, slightly
 730 over half the patients (51%) had a diastolic reading greater than
 731 110 mmHg associated with a systolic reading less than 200 mmHg.

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

736 Neutropenia and Infection

737 An increased incidence of neutropenia has been reported in patients
 738 receiving AVASTIN and chemotherapy compared to chemotherapy alone.
 739 In Study 1, the incidence of NCI-CTC Grade 3 or 4 neutropenia was
 740 increased in patients with mCRC receiving IFL+AVASTIN (21%)
 741 compared to patients receiving IFL alone (14%). In Study 5, the incidence
 742 of NCI-CTC Grade 4 neutropenia was increased in patients with NSCLC
 743 receiving PC plus AVASTIN (26.2%) compared with patients receiving
 744 PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC
 745 plus AVASTIN vs. 1.8% for PC alone). There were 19 (4.5%) infections
 746 with NCI-CTC Grade 3 or 4 neutropenia in the PC plus AVASTIN arm of

747 which 3 were fatal compared to 9 (2%) neutropenic infections in patients
748 receiving PC alone, of which none were fatal. During the first 6 cycles of
749 treatment the incidence of serious infections including pneumonia, febrile
750 neutropenia, catheter infections and wound infections was increased in the
751 PC plus AVASTIN arm [58 patients (13.6%)] compared to the PC alone
752 arm [29 patients (6.6%)].

753 Proteinuria

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

757 Immunogenicity

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

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

772 Metastatic Carcinoma of the Colon and Rectum

773 The data in Tables 4 and 5 were obtained in Study 1. All NCI-CTC
774 Grade 3 and 4 adverse events and selected NCI-CTC Grade 1 and 2
775 adverse events (hypertension, proteinuria, thromboembolic events) were
776 reported for the overall study population. The median age was 60, 60%

777 were male, 79% were Caucasian, 78% had a colon primary lesion, 56%
 778 had extra-abdominal disease, 29% had prior adjuvant or neoadjuvant
 779 chemotherapy, and 57% had ECOG performance status of 0. The median
 780 duration of exposure to AVASTIN was 8 months in Arm 2 and 7 months
 781 in Arm 3. Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse
 782 events, which occurred at a higher incidence ($\geq 2\%$) in patients receiving
 783 bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are
 784 presented in Table 4.

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

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

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

785

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

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

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

789

Table 5 (cont'd)
NCI-CTC Grade 1–4 Adverse Events in Study 1
 (Occurring at Higher Incidence ($\geq 5\%$) 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%)

790

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

Table 6
NCI-CTC Grade 3–5 Non-Hematologic and
Grade 4–5 Hematologic Adverse Events in Study 3
(Occurring at Higher Incidence ($\geq 2\%$)
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%)

802

803 **Non-Squamous, Non-Small Cell Lung Cancer**

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

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

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

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

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

814

815 Other Serious Adverse Events

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

819 *Body as a Whole: polyserositis*

820 *Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic*
821 *ulceration*

822 *Hemic and lymphatic: pancytopenia*

823 *Respiratory: nasal septum perforation*

824 OVERDOSAGE

825 The highest dose tested in humans (20 mg/kg IV) was associated with
826 headache in nine of 16 patients and with severe headache in three of
827 16 patients.

828 DOSAGE AND ADMINISTRATION

829 Do not initiate AVASTIN until at least 28 days following major surgery.

830 The surgical incision should be fully healed prior to initiation of
831 AVASTIN.

832 Metastatic Carcinoma of the Colon or Rectum

833 AVASTIN, used in combination with intravenous 5-FU-based
834 chemotherapy, is administered as an intravenous infusion (5 mg/kg or
835 10 mg/kg) every 14 days.

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

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

840 Non-Squamous, Non-Small Cell Lung Cancer

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

843 Dose Modifications

844 There are no recommended dose reductions for the use of AVASTIN.

845 If needed, AVASTIN should be either discontinued or temporarily

846 suspended as described below.

847 AVASTIN should be permanently discontinued in patients who develop

848 gastrointestinal perforation (gastrointestinal perforation, fistula formation

849 in the gastrointestinal tract, intra-abdominal abscess), fistula formation

850 involving an internal organ, wound dehiscence requiring medical

851 intervention, serious bleeding, a severe arterial thromboembolic event,

852 nephrotic syndrome, hypertensive crisis or hypertensive encephalopathy.

853 In patients developing RPLS, discontinue AVASTIN and initiate

854 treatment of hypertension, if present. (See **WARNINGS:**

855 **Reversible Posterior Leukoencephalopathy Syndrome.**)

856 Temporary suspension of AVASTIN is recommended in patients with

857 evidence of moderate to severe proteinuria pending further evaluation and

858 in patients with severe hypertension that is not controlled with medical

859 management. The risk of continuation or temporary suspension of

860 AVASTIN in patients with moderate to severe proteinuria is unknown.

861 AVASTIN should be suspended at least several weeks prior to elective

862 surgery. (See **WARNINGS: Gastrointestinal Perforation and**

863 **Wound Healing Complications and PRECAUTIONS: Surgery.**)

864 AVASTIN should not be resumed until the surgical incision is fully

865 healed.

866 Preparation for Administration

867 AVASTIN should be diluted for infusion by a healthcare professional

868 using aseptic technique. Withdraw the necessary amount of AVASTIN to

869 obtain the required dose and dilute in a total volume of 100 mL of 0.9%

870 Sodium Chloride Injection, USP. Discard any unused portion left in a

871 vial, as the product contains no preservatives. Parenteral drug products

872 should be inspected visually for particulate matter and discoloration prior
873 to administration.

874 Diluted AVASTIN solutions for infusion may be stored at 2°C–8°C
875 (36°F–46°F) for up to 8 hours. No incompatibilities between AVASTIN
876 and polyvinylchloride or polyolefin bags have been observed.

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

879 **Administration**

880 **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial
881 AVASTIN dose should be delivered over 90 minutes as an IV infusion
882 following chemotherapy. If the first infusion is well tolerated, the second
883 infusion may be administered over 60 minutes. If the 60-minute infusion
884 is well tolerated, all subsequent infusions may be administered over
885 30 minutes.

886 **Stability and Storage**

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

890 **HOW SUPPLIED**

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

894 **Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN**
895 **(25 mg/mL). NDC 50242-060-01**

896 **Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN**
897 **(25 mg/mL). NDC 50242-061-01**

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125085 / S-091

SUMMARY REVIEW

Division Director Decisional Review

Date	February 21, 2008
From	Patricia Keegan <i>Patricia Keegan 2-22-08</i>
Subject	Division Director Summary Review
BLA # Supp #	BL STN 125085.91
Proprietary / Established (USAN) names	Avastin® (bevacizumab)
Dosage forms / strength	Solution for infusion, 25 mg/mL, in 4 mL and 16 mL, single-use vials
Proposed Indication(s)	AVASTIN, in combination with taxane-based chemotherapy, is indicated for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer.
Recommended Action:	Complete Response

1. Introduction to Review

The application contains the results of two randomized, open-label, multicenter trials assessing the safety and efficacy of Avastin in combination with standard chemotherapy for second- or third-line treatment of metastatic breast cancer (Study AVF2119g) and for first-line treatment of metastatic breast cancer (Study E2100). Both studies were initiated prior to the approval of Avastin in Feb. 2004. Study AVF 2119g was conducted by Genentech and identified as a trial intended to support labeling claims for bevacizumab. The AVF2119g study enrolled 462 women receiving chemotherapy for second- or third-line treatment of metastatic breast cancer. This study failed to demonstrate an effect on either progression-free survival as determined by an endpoint review committee that was masked to treatment (the primary study endpoint) or overall survival. Study E2100 was conducted under a National Cancer Institute-sponsored IND. And enrolled 772 women receiving chemotherapy for first-line treatment of metastatic breast cancer. Genentech identified E2100 as an additional trial intended to support labeling claims for Avastin. In contrast to Study AVF2119g, Genentech did not meet with FDA to reach agreement on the design of Study E2100 prior to study initiation. FDA's recommendation for protocol modifications to strengthen confidence in the primary endpoint (progression-free survival [PFS]) through determination of the effect on PFS by an independent group, masked to treatment assignment, was not implemented during the conduct of the trial. Retrospective analyses by an endpoint review team masked to treatment assignment to independently confirm the E2100 results was marred by substantial loss to follow-up prior to the independent endpoint review team's confirmation of disease progression.

Major issues arising during this application were evidence of a treatment effect in only one of two trials and uncertainty regarding the magnitude of the effect on progression-free survival in the single positive trial. This uncertainty is largely driven by substantial loss-

to-follow-up prior to confirmation of the treatment effect on PFS by an independent group masked to treatment assignment. The lack of effect on overall survival also raises questions about the reported magnitude of effect on PFS and lends credence to the possibility that the treatment effect on PFS has been overestimated.

This application represents the first approval for first-line treatment of metastatic breast cancer in recent times (last 25 years) in which an effect on PFS has not been supported by an effect on or trend towards improved survival. In this application, demonstration of an improvement in progression-free survival is proposed as a direct clinical benefit. This is consistent with use of PFS as the basis for approval in patients with more extensively pre-treated metastatic breast cancer. The recommendation for issuance of a complete response letter requesting submission of the results of additional trials (RIBBON 1 and AVADO) is not based on use of progression-free survival as the sole measure of clinical benefit. Rather, the recommendation is based on the applicant's failure to characterize the magnitude of the treatment effect, which is necessary for the determination of the relative benefits given the known risks of Avastin.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Avastin was first approved in Feb. 2004 for use in combination with intravenous, 5-fluorouracil-based, chemotherapy regimens for the initial treatment of metastatic colorectal cancer, based on a robust improvement in overall survival and supported by prolongation of time-to-disease-progression. Subsequent labeling expansion to include use in combination with standard chemotherapy regimens for second-line treatment of metastatic colorectal cancer and for initial treatment of locally advanced or metastatic non-small cell, non-squamous cell lung cancer were also based on demonstration of improved survival.

The development program for Avastin in the treatment of metastatic breast cancer included a 75-patient phase 1-2 study of single agent therapy in patients with recurrent/progression metastatic breast cancer (AVF0776g), a randomized, multicenter, 462-patient study of capecitabine alone versus capecitabine plus Avastin for second- and third-line treatment of metastatic breast cancer (AVF2119g) and a randomized, multicenter, 722-patient, NCI-cooperative group-sponsored study of paclitaxel alone versus paclitaxel plus Avastin in the initial treatment with cytotoxic chemotherapy for metastatic breast cancer (E2100).

Study AVF2119g, was conducted by Genentech and intended to support labeling expansion for use in metastatic breast cancer. Genentech met with FDA prior to study initiation to reach agreement on study design and endpoints. The study results, which were made available after the initiation of the E2100 study, did not provide evidence of effects of Avastin on either progression-free survival or on overall survival. At FDA's request, the results of this trial were submitted in the efficacy supplement as relevant to the evaluation of Avastin in the treatment of metastatic breast cancer.

The protocol for E2100 was submitted to an NCI-sponsored IND. FDA and Genentech did not meet and reach agreement on the design of the E2100, particularly with respect to independent and masked verification of the primary endpoint PFS, prior to study initiation.

FDA issued letters on May 17, and October 24, 2002 regarding deficiencies in the design of Study E2100 for the purpose of supporting expanded labeling claims. Genentech met with FDA on Oct. 28, 2004 to discuss the adequacy of proposed modifications of the statistical analysis plan and acceptability of the primary endpoint. The E2100 study was reported to have crossed a boundary at interim analysis conducted in February 2005 and the initial results were reported at ASCO in May 2005. The results of the E2100 study were submitted to FDA in an efficacy supplement to the license application (BL STN 125085.91) on May 23, 2006.

The results of the E2100 trial were also submitted to the EMEA and resulted in an approval for the labeling expansion on March 29, 2007. The approval was based on the evidence of the effect on progression-free survival in the Avastin-containing arm compared to those receiving paclitaxel alone reported in that trial.

3. CMC/Microbiology/Device

CMC issues in this application were limited to request for categorical exclusion, which was granted. The product used in the clinical trial was an investigational product, with manufacturing information contained under IND 7023. This same investigational product was administered under IND 7023, and utilized in the clinical development program supporting the initial approval of bevacizumab. No facilities inspection was required for this application and there were no issues relevant to CMC identified during the course of the review of this supplement.

4. Nonclinical Pharmacology/Toxicology

As a supplemental application, no non-clinical data were submitted or required in support of this application. The dose and schedule of Avastin used in this development program has been studied under prior approvals and the patient population studied did not raise new concerns for which non-clinical studies would be required.

5. Clinical Pharmacology/Biopharmaceutics

The pharmacokinetic profile for the dose and schedule of Avastin for which approval is sought (10 mg/kg) was evaluated in AVF0766g, a dose-ranging, single arm study of 3, 10, or 20 mg/kg of Avastin in patients with metastatic breast cancer. The pharmacokinetic profile is consistent with current labeling and did not require modification of product labeling. Assessment of drug-drug interactions between paclitaxel and Avastin based on Study AVF0757g were evaluated in the application supporting use for treatment of non-small-cell, non-squamous lung cancer (BL STN 125085.85). With the approval of the 125085.85 supplement on Oct. 11, 2006, Genentech agreed to conduct a study to assess the impact of Avastin on the QT interval (PMC #5 of the Oct. 11, 2006 approval letter). The patient population studied did not raise new concerns for which further characterization of clinical pharmacology would be required.

6. Clinical/Statistical

6.1. General Discussion

The elements of the clinical program and pre-submission activities are discussed in earlier sections of this summary memorandum. The issues with regard to the design of the trial are primarily centered on the failure to prospectively plan for verification of the results by a group masked to treatment assignment, in order to control for potential bias in assessment in the primary analysis of progression-free survival, resulting in substantial missing data in the independent analysis and uncertainty regarding the magnitude of the treatment effect. As discussed in the Guidance of Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007), randomized trials are “essential” in studies assessing effects on time-to-event endpoints such as progression-free survival and blinding of treatment assignment preferred and blinded review for determination of the endpoint recommended. The acceptability of this endpoint for either accelerated or regular approval is “highly dependence of other factors such as effect size, effect duration...”.

As noted in Dr. Pai-Scherf’s and Dr. Lu’s reviews, there were substantial amounts of missing information for the primary analysis of IRF-determined PFS, as summarized in the table below.

Type of missing data	Paclitaxel + Avastin (n=368)	Paclitaxel (n=354)
ECOG Assessment		
• # patients with no disease at study entry	0	1(0.3%)
• # patients with no measurable disease at study entry	60 (16.3%)	61 (17.2%)
• # patients who received alternative therapy prior to ECOG-verified disease progression	81 (22%)	76 (21.5%)
IRF Analysis		
• # patients with no scans submitted to IRF	38 (10.3%)	25 (9.9%)
• # patients who were not evaluable for disease at baseline	43 (11.7%)	38 (10.7%)
• Not followed until IRF-documented progression or until end of study*	247 (34%)	
▪ % patients with no scans or other information	6%	
▪ % patients who began alternative therapy prior to IRF-documented disease progression	11%	
▪ patients with no follow-up after ECOG-determined progression but prior to IRF-determined progression	12%	
▪ patients lost-to-follow-up	5%	

The impact of the missing data is contingent on the imputations for the missing information. Below are the sensitivity analysis conducted by the sponsor, as pre-specified in the supplemental statistical analysis plans of May 14, 2007. Additional worst comparisons as performed by Dr. Lu result in elimination of the treatment effect altogether. While worst-comparisons are unlikely to represent truth, many of the comparisons below are likely to

underestimate bias by handling missing data in the two arms according to the same assumptions. Regardless, due to the extent of missing data, the true treatment effect remains unknown. It is likely that the treatment effect reported by the analysis of PFS by either ECOG- or IRF-determination overestimates the true treatment effect.

	Median PFS in months		Hazard Ratio
	Paclitaxel + Avastin (n=368)	Paclitaxel (n=354)	
ECOG – original submission	13.3	6.7	0.48
ECOG- 8/23/07 re-submission	11.4	5.8	0.42 (0.34, 0.52)
IRF- primary analysis	11.3	5.8	0.48 (0.39, 0.61)
IRF- sponsor’s prespecified sensitivity analysis 1	11.2	5.8	0.49 (0.39, 0.62)
IRF- sponsor’s prespecified sensitivity analysis 2	12.8	6.7	0.48 (0.37, 0.60)
IRF- sponsor’s prespecified sensitivity analysis 3	9.2	5.0	0.46 (0.38, 0.56)
IRF- sponsor’s prespecified sensitivity analysis 4	9.2	5.8	0.60 (0.48, 0.74)
Sponsor’s worst comparison analysis	8.2	5.8	0.78 (0.64, 0.95)

Much of the discussion regarding the acceptability of full approval based on progression-free survival as discussed by the ODAC rested on the reported magnitude of effect (a 5.5 month improvement in median PFS in Avastin-treated patients compared with controls). However, with additional data clean-up and different methods for handling of missing data in the analyses which were pre-specified and conducted by ECOG and Genentech, the estimated median PFS in the Avastin-treated arm varies as much as 5.1 months (with reported estimates of 13.3 to 8.2 months), which constitutes nearly half the treatment effect. Similarly, the difference in estimated median PFS varies from 6.6 to 2.4 months. Given the instability in the estimated values primarily due to the large amounts of missing data, it is not possible to accurately convey treatment effects to patients and healthcare providers in order to permit a reasonable judgment of relative risks and benefits.

It should also be noted that the second trial in the clinical development program, AVF2119g, failed to demonstrate an improvement in either progression-free survival (HR 0.98, p=0.86) or overall survival (HR 1.08, p=0.63) among 462 patients receiving second- or third-line treatment for metastatic breast cancer. This trial did demonstrate an improvement in overall response rate, as did E2100, however in contrast to E2100, the increase in response rate was off-set by the short durability of such responses. FDA commonly considers trials in closely related clinical settings to provide support in the determination of clinical benefit. The converse should also hold true, i.e., that the lack of benefit in the AVF 2119g trial detracts from confidence of overall activity in breast cancer and in confidence in the accuracy of the treatment effects reported in E2100.

6.2. Efficacy [see also the reviews by Drs. Lee Pai-Scherf and Laura (Hong) Lu]

6.2.1. Dose identification/selection and limitations

The dose of Avastin used in the primary study supporting efficacy (E2100) was 15 mg/kg every 21 days. This dose and schedule was studied under a prior efficacy supplement supporting approval for treatment of non-small-cell, non-squamous cell lung cancer. The majority of the studies supporting approval have utilized regimens of every 2 or every 3 weeks at doses of 10 and 15 mg/kg respectively, for an average weekly dose of 5 mg/kg/week. This average dose is tolerable against a background of cytotoxic chemotherapy and was selected primarily based on tolerance rather than pharmacodynamic effects. It is notable that this dose level more than sufficient to bind all circulating VEGF at steady state. Because of the extensive prior experience with safety of this dose and schedule, in combination with taxane-based chemotherapy, no additional justification was of the proposed regimen was requested to support this efficacy supplement.

6.2.2. Phase 3/essential clinical studies, including design and analytic features

The primary study in support of efficacy, E2100, was a randomized, open-label, multicenter study comparing the effect of Avastin when added to a medically-accepted, standard of care, cytotoxic chemotherapy regimen for the treatment of metastatic breast cancer. The design was adequate to isolate the effect of the drug and randomization was stratified for relevant prognostic factors, however the randomization did not adjust for the presence of non-measurable disease, resulting in an imbalance between study arms for this factor which may have further confounded assessment of this endpoint. The major design flaw was failure to mask treatment assignment or to minimize the impact of unintentional biases through a prospective plan for determination of the relatively subjective (soft) endpoint of primary efficacy endpoint (progression-free survival). The subsequent agreement to retrospectively determine efficacy based on PFS as determined by an independent group masked to treatment assignment was undermined by the substantial amounts of missing data.

6.2.3. Other efficacy studies

There was one study conducted to evaluate the safety and tolerability of Avastin, AVF0776g, a phase 1-2 study in women with recurrent/relapsed metastatic breast cancer. This study provided evidence of very modest anti-tumor activity in the form of objective tumor responses.

The application also contained the results of the AVF2119g, the study originally intended to establish safety and efficacy of Avastin, in combination with standard chemotherapy for the treatment of metastatic breast cancer. This study, an open-label, multicenter, randomized (1:1) trial conducted in 462 patients, demonstrated no effect on progression-free survival or overall survival among patients receiving Avastin plus capecitabine over those receiving capecitabine alone. The study population in AVF2119g differs from that

enrolled in E2100 in that the AVF2119g subjects were more heavily pre-treated (second- and third-line vs. first-line), women with metastatic breast cancer and received a different cytotoxic chemotherapeutic agent (capecitabine rather than paclitaxel).

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions

There were substantial concerns expressed by the clinical and statistical review team with regard to the accuracy of the determination of magnitude progression-free survival effects and the lack of support in the key secondary endpoint of overall survival. It should be noted that the reviewers agree that presence of some effect on PFS has been established by consistent demonstration of the presence of an effect in all but the most draconian sensitivity analysis (worst-case scenario) with imputations for missing data. However the estimation of effect on PFS in both treatment arms is sensitive to the manner in which PFS is determined (investigator vs. IRF) as well as the various strategies for imputation of missing data. The concerns regarding whether PFS effects were sufficient to establish clinical benefit were shared by some members of the Oncologic Drugs Advisory Committee, leading to a mixed recommendation regarding approval. Based on these concerns, the results of additional studies isolating the effects of Avastin, in combination with medically-accepted cytotoxic chemotherapy regimens for first-line treatment of metastatic breast cancer, on progression-free survival have been requested to further characterize the magnitude of PFS effects.

6.2.5. Pediatric use/PREA waivers/deferrals

A request to waive the requirement to conduct pediatric studies under PREA was granted because the condition (metastatic adenocarcinoma of the breast) does not occur in children.

6.3. Safety

6.3.1. General safety considerations

The size of the population characterizing the toxicity of Avastin in combination with paclitaxel for first-line treatment of metastatic breast cancer was adequate and included 363 patients exposed to Avastin in the E2100 trial at a dose of 10 mg/kg every 14 days. The size of this database allows detection of adverse reactions occurring in at least 1% of patients treated. The toxicity data from the E2100 trial are limited to severe, life-threatening, or fatal (NCI CTC Grades 3-5) non-hematologic adverse events and NCI CTC Grades 4-5 hematologic adverse events collected in experimental and control arms and detailed descriptions only in the Avastin (experimental) arm characterizing adverse events leading to termination of treatment (dropouts) or deaths temporally related to treatment. These limitations in toxicity data collection preclude an evaluation of mild or moderate toxicities as a signal for severe or life-threatening adverse drug reactions occurring at a low frequency and modestly increased above the background rate.

These toxicity results from E2100 are supplemented by toxicity data obtained in 229 patients who received Avastin at a dose of 15 mg/kg every 21 days in Study AVF2119g. The major safety findings across both studies are similar to those observed in other controlled trials isolating the effects of Avastin, including hypertension, severe proteinuria and nephrotic syndrome, impairment of wound and tissue healing manifesting as viscus perforation and fistula formation, and hemorrhage.

In the E2100, as in the E4599 study supporting labeling expansion for first-line treatment of locally advanced or metastatic lung cancer, there was an increase in sensory neurotoxicity in the Avastin arm as compared to controls. After adjustment for cumulative dose or time on therapy leading to first event, the higher incidence of neurotoxicity remains and cannot be explained solely by higher cumulative dose of paclitaxel in the experimental arm. This will be discussed in greater detail in section 6.3.2.

6.3.2. Safety findings from submitted clinical trials

FDA requested additional analyses characterizing the time to onset of NCI CTC Grades 3-4 neurotoxicity, specifically in support of statements in the proposed labeling stating “After adjusting for duration of treatment, the rates of Grades 3-5 sensory neuropathy were comparable between the treatment arms.”

FDA requested an analysis of time-to-first sensory neuropathy event as a function of treatment cycle and as a function of cumulative paclitaxel dose. In both analyses, early differences in the incidence of first Grade 3-4 sensory neuropathy event are apparent at time points in which at least 100 patients in each arm were available for comparison. The increased rate of severe sensory neuropathy is only partially explained by longer exposure to paclitaxel. Regardless, the higher rate of neurotoxicity is observed in this combination as currently labeled and thus reflects expected toxicity under directions for use.

Per-patient incidence of first Grade 3-4 sensory neuropathy event as a function of cycle or cumulative paclitaxel dose		
	Paclitaxel + Avastin	Paclitaxel
Incidence by treatment cycle		
Cycles 1-3	2.8% (10/353)	1.2% (4/338)
Cycles 4-6	10.4% (30/288)	10.7% (23/215)
Cycles 7-9	7.9% (16/203)	9.8% (12/122)
Incidence by cumulative dose of Taxol		
1-1000 mg	3.1% (11/353)	1.5% (5/338)
1001-2000 mg	6.5% (20/309)	6.7% (19/285)
2001-3000 mg	7.2% (18/250)	4.4% (8/141)

6.3.3. Safety update

The maturity of the study results in the resubmission of Aug. 2007, led to agreement during meetings prior to the resubmission that a 120-day safety update was not required.

6.3.4. Immunogenicity

No immunogenicity assessments were conducted in Study E2100. Data from previous studies in this and other clinical settings suggest that the incidence of anti-product antibodies is low and unlikely to have effects on either safety or product efficacy.

6.3.5. Special safety concerns

The only additional safety concern was an evaluation to determine whether lack of a survival benefit was the result of an increased toxic death rate. Dr. Paischerf reviewed case reports forms to identify such deaths, given lack of narratives for the control arms. Although there was a numerical increase in toxic deaths in the Avastin arm, the number of deaths (6 of 363; 1.6% of Avastin-treated patients) is too low to impact the results of overall survival for the study population.

6.3.6. Discussion of primary and secondary reviewers' comments and conclusions

The medical officer raised concerns regarding the lack of collection of less severe adverse events, which is suboptimal for detection of signals and limits assessment of attribution of toxicity. For the severe and life-threatening adverse reactions of Avastin, the profile was consistent with that previously reported in prior approvals and is adequately described in product labeling.

6.4. Clinical Microbiology

Clinical microbiology data are not relevant to this product class and indication.

7. Advisory Committee Meeting

A meeting of the Oncologic Drugs Advisory Committee (ODAC) was convened on Dec. 5, 2007 to discuss this application. The committee was asked to discuss but not vote on the question of whether a prolongation in progression-free survival can be considered a direct measure of clinical benefit. Some members of the committee strongly expressed support for prolongation of PFS as a direct benefit. In these discussions, a delay in PFS was felt to be likely to result in delay in time to treatment-related symptoms and provide a "psychological benefit" to patients. The magnitude of benefit was also expressed as important although the Committee declined to characterize this further, indicating that if the FDA were concerned, they should seek advice from the ODAC on individual applications. The Committee also expressed concerns regarding requirement for a higher standard for first-line (requirement for effect on survival or on consistent, strong trend towards improved survival) as opposed to approval standards for second- and subsequent-line treatments for metastatic breast cancer, which has been based primarily on PFS or time-to-disease progression.

The ODAC voted on the question of whether the reported impact of Avastin in the E2100 study (HR 0.48, 5.5-month improvement in median PFS), considering the lack of effect on overall survival and additive toxicity of Avastin to standard chemotherapy, constituted substantial evidence of clinical benefit. The committee was divided on this issue; four members voting that there was and five members voted that there was not demonstration of substantial evidence of clinical benefit. The discussion of those in favor considered the reported magnitude of the effect, the possibility of subsequent therapy obscuring a survival advantage, and consistency of approval standards across first- vs. second and subsequent-line treatments for metastatic breast cancer. Those voting against this question raised concerns regarding lack of certainty in the treatment effect on PFS and lack of clarity on how a prolongation in PFS directly benefits patients.

8. Risk Minimization Action Plan

The applicant did not propose, nor did the Agency request, a risk minimization action plan. The primary toxicities of this product have been established and will be minimized primarily through description in product labeling.

9. Other Regulatory Issues

9.1. Application Integrity Policy (AIP)

There were no concerns raised regarding application integrity to suggest systematic or intentional inclusion of erroneous or misleading data.

9.2. Exclusivity/patent issues

There were no issues in this application relating to exclusivity or patent protections.

10. Financial Disclosure

There were no concerns raised by financial disclosure information submitted by study investigators, given the small number of subjects enrolled at any individual site and limited ability of any study site to impact the overall study results. There were more substantial potential conflicts of interest among the study administration and data monitoring committees, involving 30% of those who submitted disclosure reports. The impact of such conflicts on study results is unclear. Reliance on the IRF for subjective study endpoints is likely to control for sources of bias.

11. Labeling

Comments from the review team and from the consultant reviewer from DDMAC were considered and incorporated, leading to the approved physician labeling. Genentech's proposed labeling was modified as below for the reasons indicated:

Proposed indication modified to reflect that Avastin was studied in combination with paclitaxel (not all taxanes) in E2100. The proposed indication was further revised to note that demonstration of efficacy is based on PFS, not on effects on overall survival or symptom relief. This revision was based on the findings of the E2100 and to provide clarity on treatment benefits to the prescribers. In addition, the proposed indication was revised to note that Avastin is not indicated for use in patients with more refractory metastatic breast cancer, based on the results of the AVF2119g study. This change was

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also to highlight evidence of efficacy in related clinical settings to which prescribers are likely to extrapolate potential benefits.

Clinical studies section modified to with regards to E2100 results to include results of sensitivity analysis on PFS to convey uncertainties regarding treatment effect on PFS, removal of Kaplan-Meier curve, which may be misleading due to high number of dropouts and censored data, and Forrest plot displaying exploratory subset analyses of PFS removed due to their exploratory nature and because of uncertainties with regard to magnitude of PFS results in these subsets as well. In addition, labeling revised to include updated and final results of OS analysis and all analyses of based on tumor endpoints revised to reflect IRF rather than investigator determination.

Clinical studies section also modified to include the results of the AVF2119g study which demonstrates no efficacy in second- and third-line metastatic breast cancer to ensure communication of the lack of efficacy to patients and healthcare providers.

Warnings: Congestive Heart Failure subsection and Adverse Reactions section modified to include new information on adverse reactions in women with breast cancer, where such data were different (either higher incidence or severity) than previously described. Tabular results of Grade 3-5 adverse reactions from study E2100 removed and replaced with text to summarize unique findings in this study for brevity. Statements attributing _____ removed due to the exculpatory nature and because higher rates of neurotoxicity are also observed at early as well as late in treatment.

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12. DSI Audits

Given the small percentage of study subjects enrolled at individual study sites, the auditing of safety information by Genentech at FDA's request as contained in the resubmission of August 23, 2007, and the verification of the primary study endpoint (PFS) by an independent endpoint review committee, additional auditing of clinical studies sites by the Division of Scientific Integrity were not considered necessary for this application.

13. Conclusions and Recommendations

13.1. Regulatory action

My recommendation is that a complete response letter be issued requesting the results of the two ongoing, randomized, multicenter clinical trials designed to establish the magnitude of treatment effect for first-line chemotherapy treatment of metastatic breast cancer. The high-level results of the AVADO trial, a randomized, placebo-controlled, multicenter trial conducted by Roche in Europe, are available and review of the clinical study results should provide confirmation of and greater confidence in the magnitude of effects on PFS in the proposed indicated populations.

The results of the E2100 and AVF2119g trials do not provide consistent findings with regard to the treatment effects of Avastin as an adjunct to standard chemotherapy for metastatic breast cancer. In AVF2119g, a more heavily pre-treated population, there was not substantial evidence of a treatment effect on a measure of clinical benefit. Study

AVF2119g demonstrated drug activity through improved response rates which was off-set by the lack of durability of such responses. In the E2100 trial, treatment effects were shown on progression-free survival and partial tumor response rates but not on overall survival. In addition, the magnitude of the treatment effect on PFS reported in E2100 is uncertain due to the substantial number of patients (34% of the study population) for whom presence disease progression could not be confirmed by an independent group of radiologists and oncologists masked to treatment assignment (IRF). Among the 194 patients (27% of the study population) for whom there was agreement on presence of disease recurrence, in 86 (44%), the date of recurrence differed by more than 6 weeks between investigators and the IRF. With the inability to verify the treatment findings in a substantial portion of the patients, there is a lack of certainty in the magnitude of the treatment effect. Although sensitivity analyses with imputations for missing data continue to show a significant difference in PFS favoring the Avastin-treated arm, the magnitude of the treatment effect varies by greatly (hazard ratios ranging 0.48 to 0.78) and estimates of the projected differences also vary greatly, with 2.4 to 5.5 month differences in median PFS depending on the analytic approach. Given the uncertainty in treatment effect, determination of the benefit-risk may range from marginal to substantial advantages favoring treatment. The safety profile of Avastin in this clinical setting is similar to that observed in patients with metastatic colorectal cancer and metastatic lung cancer. The risks in these settings were deemed acceptable given substantial impact on survival and time to disease progression. In this clinical setting, the risks of treatment are likely to be considered acceptable by this patient population even with a modest (2.4 month) prolongation in median progression-free survival, as estimated in one sensitivity analysis. However smaller differences which may also exist given the uncertainty of the accuracy of estimation of the treatment effect, may not be considered reasonable to patients and physicians. Because this judgment by patients and physicians can only be made with reliable estimates of treatment effects, the treatment effect should be verified in additional studies to permit individualized determinations of the risks and benefits.

The members of the clinical and statistical review teams expressed reservations regarding the magnitude of the treatment effect; these concerns were addressed primarily through multiple sensitivity analyses. In addition, the team noted the lack of an effect on survival. There is agreement among the review staff that there is no evidence of an effect on survival in E2100 and that it is unlikely that post-treatment interventions obscured such an effect, given the lack of drugs known to confer survival advantages in metastatic breast cancer after failure of anthracycline and taxane therapy. Since many of the study patients were treated and progressed prior to marketing approval was granted for Avastin, and given the failure to show a treatment effect on survival in later stage disease in AVF2119g, there is assurance that post-study treatment with Avastin could not obscure survival effects of Avastin in the first-line setting.

An alternative consideration for regulatory action is an accelerated approval based on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of any necessary studies to establish and define the degree of clinical benefits to patients. Such an approval would carry a requirement to study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the

relation of the observed clinical benefit to ultimate outcome. This would be considered when "the clinical endpoint leaves sufficient doubt as to the ultimate value of the effect". This regulatory provision also "serves as a reminder that for life-threatening diseases, the ultimate aim of therapy is improved survival as well as improved symptoms." While the lack of effect on survival has been established, it is clear from discussions at the Dec. 5, 2007 ODAC meeting that this clinical endpoint does carry some uncertainty as to whether prolongation of PFS has an impact on the ultimate outcomes of either health-related quality of life or delay in time to symptomatic progression as expressed by several of the members. As expressed by some committee members, the magnitude of the effect was a strong driver of the determination of direct clinical benefit and thus one may infer that uncertainty in the magnitude of the effect introduces uncertainty regarding the presence of clinical benefit. I do not believe that the circumstances in this situation are consistent with the intent of this provision of the accelerated approval regulations to offer regulatory flexibility and discretion. Specifically, this application is supported by evidence of efficacy in a single study which did not adequately control for bias of a subjective endpoint because the independent verification of the endpoint was impacted by missing data and the lack of replication of treatment effects in a closely related, though not identical, clinical setting.

13.2. Safety concerns to be followed postmarketing: none

13.3. Risk Minimization Action Plan, if any: none

13.4. Postmarketing studies

13.4.1. Required studies

Two trials were identified as serving to better characterize the treatment effect on PFS, due to concerns with regard to the accuracy of the estimated treatment effect identified in the E2100 trial. These trials are:

- Ribbon 1 (also known as Study AVF3694g) conducted by Genentech, as a randomized study of Avastin in combination with chemotherapy vs. chemotherapy alone as first-line treatment of metastatic breast cancer. The primary study endpoint is PFS and secondary endpoints include overall response rate and survival. The study data will be available Q32008.
- AVADO (also known as Study BO17708) conducted by F. Hoffmann-La Roche, as a randomized study of Avastin in combination with docetaxel vs. docetaxel alone as first-line treatment of metastatic breast cancer. The primary study endpoint is PFS and secondary endpoints include overall response rate and survival. The study data will be available March 2008.

As discussed above, the requirement to conduct pediatric studies under PREA was waived because adenocarcinoma of the breast is not a disease that occurs in children.

13.4.2. Commitments (PMCs)

FDA requested that the following additional studies, further characterizing the safety and efficacy of Avastin in treatment of more heavily pre-treated breast cancer, be submitted under voluntary PMCs and Genentech agreed to provide these study results. This is particularly important given the lack of activity in second- and third-line treatment of metastatic breast cancer demonstrated in AVF 2119g. _____

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- Ribbon 2 (also know as Study AVF3693g) conducted by Genentech, as a randomized study of Avastin in combination with chemotherapy vs. chemotherapy alone as second-line treatment of metastatic breast cancer. The primary study endpoint is PFS and secondary endpoints include overall response rate and survival. The study data will be available Q32009.
- CALGB C40503 (also known as AVF3903s) being conducted by the NCI, a randomized trial of Avastin in combination with an aromatase inhibitor or tamoxifen versus an aromatase inhibitor or tamoxifen in ER+/PR+ metastatic breast cancer. The primary endpoint is PFS and secondary endpoints are overall response rate and overall survival. The trial is not yet open to accrual, thus availability of study data cannot be projected.
- AVEREL (also known as Study BO20231) conducted by F. Hoffmann-La Roche as a randomized study of Avastin in combination with Herceptin and taxane chemotherapy versus Herceptin and taxane alone in the first-line HER2+ metastatic breast. The primary endpoint is PFS and the secondary endpoints include overall response rate and overall survival. The study results will be available Q1 2001.

13.5. Summary of reviewers' comments

Dr. Lee Pai-Scherf, the clinical reviewer, has recommended accelerated approval of this application, with verification of ultimate clinical benefit to be demonstrated in two additional trials (AVADO [BO17708) and RIBBON 1 [AVF3694g]) which are required post-marketing commitments under the under 21 CFR 601 Subpart E. Dr. Laura Lu, the statistical reviewer, did not make a specific recommendation but noted concerns regarding uncertainty regarding the magnitude of the effect on PFS in Study E2100, lack of an effect on PFS in a more refractory setting in Study AVF2119g, and lack of an effect on survival in either Study E2100 or AVF2119g.

13.6. Comments to be conveyed to the applicant
See approval letter of February 22, 2008.

Appendix 1

Pre-specified sensitivity analyses per Amendment 2 (E2100 supplemental statistical analysis plan) dated May 14, 2007

5.3.1 Sensitivity Analyses

The following sensitivity analyses are designed to assess the robustness of the primary analysis.

a. Analysis 1

All PD dates immediately following a UE timepoint response should be backdated to the previous UE timepoint assessment date based on the IRF Procedure Document. However, in exceptional cases, such as when an interval scan or relevant clinical information was assessed between two non-UE timepoints and these non-UE assessments occurred within the expected time interval of 12 weeks, the oncologist may decide not to backdate the PD date. This analysis assesses the impact on the primary endpoint if the backdating of PD is done independent of the oncologist's judgment.

In Analysis 1, every PD preceded by a UE assessment, irrespective of the oncologist's rationale for not backdating the PD, will be backdated to the UE immediately preceding the PD. This serves as an extension to the primary method, as described in Section 5.2 of this document, in which the backdating of the PD date is dependent on the oncologist's review of individual patient data. PFS will be calculated based on the updated PD date and the analysis will be done as described in Section 5.3 of this document.

b. Analysis 2

To explore the possible effect of clinical oncology data on the IRF's assessment of PFS, another sensitivity analysis will be conducted based only on the independent radiographic assessments. In Analysis 2, for all patients, the PD dates will be based on the radiologist's read only, as this will have the effect of removing the clinical oncology data from the overall response assessment. Data for patients who develop missing PD dates because of this process will be censored in this analysis. PFS will be evaluated based on the updated PD dates, and all of the analyses will be done as described in Section 5.3 of this document.

5.3.2 Additional Sensitivity Analyses

The goal of the following sensitivity analyses is to evaluate the impact of missing PD dates on the primary analysis when PD assessed by the investigator, as contained in the E2100 database, is not confirmed by the IRF. Thus the PFS value, as assessed by the IRF, is censored. Potentially, this kind of censoring could lead to informative censoring. The following sensitivity analyses will be performed to assess the impact of such censoring on the primary endpoint

a. Analysis 3

In Analysis 3, all patients with missing PD dates resulting from the inability of the IRF to confirm progression will have their PD dates set as the date of the last tumor assessment +1 day. PFS will be calculated based on the updated PD dates, and all of the analyses will be done as described in Section 5.3 of this document.

b. Analysis 4 (Worst Case Analysis)

In Analysis 4, the PD dates for patients in the paclitaxel + bevacizumab arm for whom PD could not be confirmed by the IRF will be set to the date of the last tumor assessment +1 day, whereas the PD dates for patients in the paclitaxel alone arm for whom PD could not be confirmed by the IRF will remain censored. PFS will be calculated based on the updated PD dates, and all of the analyses will be done as described in Section 5.3 of this document.

Officer/Employee List
Supplement: STN 125085/91

The following officers or employees of FDA participated in the decision to approve this supplement and consented to be identified:

1. Jones, Karen
2. Keegan, Patricia
3. Kress, Sheldon
4. Pai-Scherf, Lee
5. Pazdur, Richard
6. Rieves, Rafel
7. Rothmann, Mark

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125085 / S-091

OFFICE DIRECTOR MEMO

OFFICE DIRECTOR'S MEMO

February 21, 2008

Richard Pazdur, MD
Director, Office of Oncology Drug Products



Re: STN 125085/91

Indication: Avastin in combination with paclitaxel is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer.

Avastin in Metastatic Breast Cancer: The safety and efficacy of Avastin as a treatment for first-line metastatic breast cancer was evaluated in a single trial (Study 7) that enrolled 722 women. This trial was an open-label, randomized multi-center trial comparing paclitaxel to the combination of paclitaxel plus Avastin. An additional trial (Study 8) was reviewed by the FDA. Study 8 evaluated a more refractory breast cancer population (second and third-line treatment) in a randomized open label study.

Study 7: Efficacy results

Breast cancer patients who had not received chemotherapy for locally recurrent or metastatic breast cancer were randomized to receive either paclitaxel alone or in combination with Avastin. Patients with breast cancer over-expressing HER2 were not eligible unless they had received prior therapy with Herceptin. Prior hormonal therapy for the treatment of metastatic disease was allowed. Prior adjuvant chemotherapy was also permitted. The trial's primary outcome was progression-free survival (PFS) assessed by an independent review facility (IRF). Secondary outcome measures were objective response rate (ORR) and overall survival (OS).

The study met its primary endpoint, demonstrating a statistically significant PFS improvement with the addition of Avastin to paclitaxel compared to paclitaxel alone. The median PFS on the combination arm was 11.3 compared to 5.8 months (<0.0001 , HR 0.48, 0.39, 0.61) indicating that the risk of progression or death was less than half in patients treated with Avastin plus paclitaxel. An analysis of OS disclosed a median of 26.5 months (23.7, 29.2) versus 24.8 months (21.4, 27.4) for the combination and single-agent paclitaxel, respectively. There was no significant improvement in OS ($p=0.14$ HR 0.87 (0.72, 1.05)). A statistically significant improvement in ORR was noted; 48.9 versus 22.2 % ($p<0.001$) of patients experienced responses in the Avastin plus paclitaxel arm compared to paclitaxel alone. Responses were partial responses; no complete responses were observed.

Study 8: Efficacy results

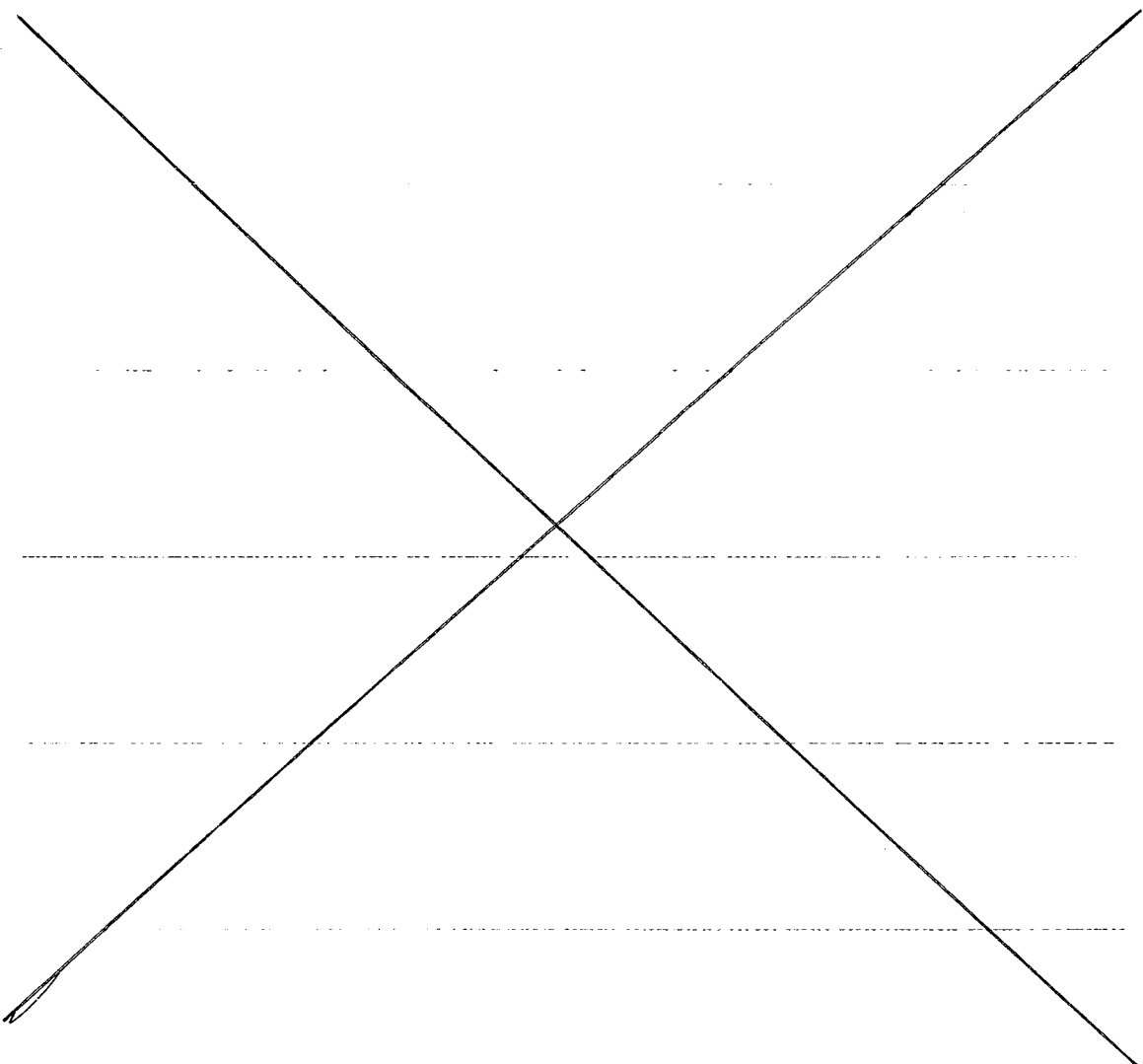
Patients (N=462) enrolled in study 8 had received prior anthracyclines and taxane therapy in the adjuvant setting or for metastatic disease and were randomized to receive either capecitabine alone or in combination with Avastin. The trial did not demonstrate a

statistically significant effect on PFS or OS. The median PFS was 4.2 months in the capecitabine alone arm and 4.9 months in the combination arm (p=0.86, HR 0.98). The median OS was 14.5 and 15.1 months (HR=1.08), respectively, for the single agent versus combination arm. These results are included in product labeling. In addition, the following statement is included in INDICATIONS AND USAGE: "Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane therapy for metastatic disease."

Study 7: Adverse Reactions (AEs)

Please refer to the primary clinical review and Avastin product labeling for a complete discussion of adverse reactions. There was a 20.2% increase in grade 3-5 toxicities and a 1.7% treatment-related death associated with the Avastin plus paclitaxel treatment. Grade 3 AEs occurred in 39 versus 56%, grade 4 AEs in 9 versus 12%, and grade 5 in 2 versus 3% of patients treated with single-agent paclitaxel versus Avastin plus paclitaxel.

(NON-PUBLIC INFORMATION)



b(4)

b(4)

Discussion

Considerable discussions within the Agency, at ODAC meetings, with international regulatory agencies, and in workshops conducted with oncology professional societies have focused on the use of PFS as a regulatory endpoint. Although an improvement in OS remains the gold standard, PFS and time-to-progression (TTP) in advanced disease and disease-free survival (DFS) in the adjuvant setting, have been advocated for approval endpoints in oncology indications. The OS analysis may be confounded by cross-over and/or subsequent therapies. PFS, measured prior to the introduction of other post-progression therapies, may more accurately depict a treatment's therapeutic effect. PFS and DFS have been suggested either as "surrogates" for clinical benefit (survival improvement) or as clinical benefit per se indicating that a delay in disease progression is of direct benefit to patients.

The Agency has accepted PFS as a primary registration endpoint in the recent past, including approvals for renal cell cancer (Nexavar), multiple myeloma (Revlimid), gastrointestinal stromal tumors (Sutent), ovarian cancer (gemcitabine), breast cancer (paclitaxel, ixabepilone and lapatinib). These breast cancer approvals have been in more heavily pre-treated patients than in the first-line indication being sought with Avastin. The EMEA has advocated for the use of PFS as a primary endpoint in first-line settings because of the concern that subsequent therapies may confound OS analysis. The EMEA has approved this Avastin application in the first-line therapy of breast cancer over a year ago using PFS as the primary registration endpoint.

At the ODAC meeting held in December 2006, discussion focused on the potential implications of "lines of therapy." Several members commented that with the availability of a greater number of drugs in the treatment of both adjuvant and advanced breast cancer and with the introduction of multiple drugs in the adjuvant setting, the distinction between first-line and subsequent lines of therapy may be "blurred", "artificial" or lacking the clinical importance once held. ODAC members agreed that when PFS would be used as the primary registration endpoint, data on OS must be collected to ensure that a detrimental effect on OS is not observed. OS is an efficacy and safety endpoint.

In the current application, the HR for OS was 0.869 (95% CI 0.722, 1.046) indicating that a detrimental effect on OS was unlikely with the addition of Avastin to paclitaxel. Although not pre-specified endpoints, the 1-year survival (81 vs 74%) and 2-year survival (55 vs 50%) favored the Avastin plus paclitaxel arm compared to single-agent paclitaxel. Trial 7 had only 25% power to detect a 3-month improvement in median OS.

There was agreement between investigator-assessed endpoints (both PFS and ORR) and the independent radiographic facility (IRF) for Study 7. The investigator-assessed ORR was 48% versus 22.2% ($p < 0.0001$); the IRF review was 49.8% versus 22.2% ($p < 0.0001$) for the Avastin-containing arm versus single-agent paclitaxel treatment, respectively. The median PFS was 5.8 months for the paclitaxel arm and 11.4 months for

the Avastin-containing treatment (HR 0.421, $p < 0.0001$) when assessed by the investigator. The median PFS was 5.8 months for the paclitaxel arm and 11.3 months for the Avastin-containing treatment (HR 0.483, $p < 0.0001$) when assessed by the IRF. Because of the close agreement between the two assessments (investigator and IRF), systemic bias seems unlikely.

A sensitivity analysis demonstrated a significant benefit was retained by the Avastin arm when the investigator assessed a progression event that was subsequently not confirmed by the IRF. In this sensitivity analysis, paclitaxel alone patients were censored, whereas those on the Avastin arm were deemed as progression. In this analysis, the median PFS was 5.8 months for patients receiving single-agent paclitaxel and 9.2 months for the Avastin-containing arm (HR 0.60, $p < 0.0001$). An additional sensitivity analysis was performed examining patients who were lost to follow-up for the PFS analysis due to having discontinued tumor assessment and/or having non-protocol therapy prior to an investigator's determination of progression. These patients on the Avastin plus paclitaxel arm were considered to have disease progression. The disease progression date was considered to be the patient's last contact date plus one day. The PFS data for the corresponding patients on the paclitaxel alone arm remained censored at the last date of contact. This analysis showed a HR of 0.78 ($p = 0.0153$) indicating a retention of Avastin's benefit.

The FDA clinical and statistical reviews and ODAC presentations state that Avastin's effect on the PFS endpoint is robust, but question the effect's magnitude. With the acceptance of PFS as a registration endpoint for oncology trials, the Agency and sponsors are developing greater experience with the use of independent radiographic/clinical endpoint assessment and handling of missing data. In Trial 7, 87% of patients had adequate information for IRF review. There was no evidence of an imbalance or bias in missing data between the two treatment arms (86% versus 87% .) Pre-specified sensitivity analyses corroborate the maintenance of a treatment effect in handling missing data. Recent applications have had missing data similar to that observed in the current Avastin application: Tykerb had 13% of missing data for tumor evaluation for TTP and Nexavar had 5% baseline scans missing.

Although the Sponsor agrees that some patient-level discordance occurred, they assert that the PFS Kaplan-Meier curves comparing the investigator and IRF assessments of progression provide evidence that systematic bias was not present. During the ODAC meeting, FDA questioned the adequacy of patient follow-up since data for 37% of patients were censored for PFS more than 90 days prior to data cut-off. In a post-ODAC meeting, the Sponsor disagreed with this assertion. They state that only 5% of patients were censored more than 90 days for incomplete follow-up. The observed censoring occurred because of the introduction of non-protocol anti-neoplastic therapy prior to progressive disease (this censoring was specified in the protocol) or "anticipated consequences of having an IRF (missing data and censoring due to lack of confirmation)." As noted above, investigator-determined progressive disease that was subsequently not confirmed by the IRF did not impact PFS according to a planned sensitivity analysis.

Although the addition of Avastin to paclitaxel resulted in an increase in Grade 3 to 5 AEs, the Sponsor suggested additional considerations in the interpretation of the Trial 7 risk/benefit analysis. Patients receiving the Avastin-containing arm received more

therapy (median 10 cycles) over a longer period of time than patients receiving single-agent paclitaxel (median 6 cycles). In addition, there was no difference between treatment-related discontinuation of therapy due to toxicity, death, or other reasons (19% on the Avastin-containing treatment; 20% on single-agent paclitaxel). Most patients discontinued therapy because of disease progression.

The imbalances between Grade 3 to 5 AEs were primarily due to grade 3 AEs (grade 3, 39.4 vs. 55.6%; grade 4, 9.2 vs. 12.1%, grade 5, 2.0 vs. 3.0%). Asymptomatic hypertension or proteinuria contributed to the 16.2% increase in grade 3 AEs. If these were excluded, the imbalance would be 11.6%.

FDA and the Sponsor agree that 1.7% (6 patients) of the Avastin-treated patients died as a result of therapy; this statement is included in proposed product labeling. The Sponsor states that this percentage of treatment-related deaths should be compared to the overall 7% absolute improvement in 1-year survival in Avastin-treated patients in formulating a risk/benefit analysis. No new safety signals were identified in these registration trials.

Although Trial 7 and AVADO (both first-line metastatic trials) met their primary endpoint of improving PFS (and secondary endpoint of ORR), Trial 8 failed to demonstrate a statistically significant improvement of PFS. Trial 8 had a more heavily pre-treated patient population. Whereas, none of the Trial 7 patients had prior anthracycline or taxane therapy for metastatic disease, over 80% of Trial 8 patients had these prior therapies. Only 2% of Trial 7 patients were HER2 positive; 27% of Trial 8 patients were HER2 positive.

A plausible explanation of the difference in the results of trial 7 and 8 may relate to the Avastin's action. VEGF blockade may have a greater therapeutic role in patients who are not as heavily pre-treated. Previous approvals of Avastin (non-small cell lung cancer and colorectal cancer) where OS advantages have been observed have been in the first-line setting for metastatic disease where patients are not heavily pretreated with chemotherapy.

REGULATORY ACTION: Approval (subpart E)

This application is granted accelerated approval. The addition of Avastin to paclitaxel is an improvement over available therapy (single-agent paclitaxel) in a serious or life-threatening disease (metastatic breast cancer). Further information of Avastin's effect on the ultimate clinical benefit, survival, is desired prior to converting this application to regular approval.

This is the third approval for Avastin. Prior approvals include its use with intravenous 5-fluorouracil-based chemotherapy for the first or second-line treatment of patients with metastatic carcinoma of the colon or rectum and its use in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.

The current application demonstrates a robust effect on PFS and response rate (secondary endpoint). Although not reviewed by the Agency, preliminary data from the AVADO trial also showed an improvement in PFS and ORR. Trial 7 and 8 did not disclose any new safety signals. Over 10,000 patients have been treated with Avastin in clinical trials

and over 200,000 patients have been treated with commercial drug. The use of Avastin with paclitaxel is associated with increased AEs and therapy-related deaths that are described in product labeling. Despite the 1.7% treatment-related deaths occurring in the first year, a 7% improvement in 1-year survival was observed with the addition of Avastin to paclitaxel.

The Sponsor has agreed to conduct and submit the following studies:

Study BO17708: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Docetaxel in Comparison with Docetaxel Plus Placebo as First-Line Treatment for Patients with HER2-Negative Metastatic Breast Cancer;

Study AVF3694g: A Multicenter, Phase 3, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer;

Study AVF3693g: A Phase 3, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Treated Metastatic Breast Cancer;

Study BO20231: A Randomized, Open-Label, 2-Arm, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Trastuzumab/Docetaxel Compared with Trastuzumab/Docetaxel Alone as First Line Treatment for Patients with HER2 Positive Locally Recurrent or Metastatic Cancer;

CALGB 40503: "A Endocrine Therapy in Combination with Anti-VEGF Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Endocrine Therapy Alone or Endocrine Therapy plus Bevacizumab for Women with Hormone-Receptor Positive Advanced Breast Cancer.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125085 / S-091

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: 125085.91
Drug Name: Avastin/bevacizumab
Indication(s): Breast Cancer, first-line
Applicant: Genentech
Date(s): Submission Date: 23-AUG-07, PDUFA Date: 23-FEB-08
Review Priority: Priority
Medical Division: Division of Biological Oncology Products
Clinical Reviewer: Lee Pai-Scherf, MD *Lee Pai Scherf Feb 22, 2008*
Acting Team Leader: Patricia Keegan, MD *P. Keegan 2-22-08*
Division Director: Patricia Keegan, MD
Project Manager: Sharon Sickafuse
Biometrics Division: Biologics and Therapeutics Statistical Staff (HFD-711)
Statistical Reviewer: Hong Lu, PhD
Concurring Reviewers: Mark Rothmann, PhD, Statistical Team Leader, Aloka, Chakravarty, Ph.D., Director

CLINICAL REVIEW

Application Type sBLA
Submission Number 125085\91
Submission Code PAS

Letter Date August 23, 2007
Stamp Date August 23, 2007
PDUFA Goal Date February 23, 2008

Reviewer Name Lee Pai-Scherf, MD
Review Completion Date February 22, 2008

Established Name Bevacizumab
(Proposed) Trade Name Avastin®
Therapeutic Class TBP Antiangiogenic
Applicant Genentech Inc

Priority Designation P

Formulation Intravenous
Dosing Regimen 10 mg/kg every 2 weeks
Indication In combination with paclitaxel for
the treatment of locally recurrent
or metastatic breast cancer, in
combination with paclitaxel
Intended Population Patients who have not received
chemotherapy for locally recurrent or
metastatic breast cancer

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer of the Division of Biologic Oncology Drug Products (DBOP), Center for Drug Evaluation and Research (CDER), FDA recommends accelerated approval of supplemental biologic licensure application (sBLA) STN 12508591 for the use of bevacizumab in combination with paclitaxel for first-line treatment of patients with locally recurrent or metastatic breast cancer.

The sBLA consisted of a single randomized controlled unblinded trial in first-line breast cancer. A total of 722 patients with metastatic breast cancer who had not received prior chemotherapy for their metastatic disease were randomized to receive bevacizumab plus paclitaxel or paclitaxel alone.

The assessment of benefit in this application is based on the endpoint of progression free survival. The recommendation is based on the review of the clinical data, which supports the conclusion that bevacizumab plus paclitaxel delays time to disease progression and increases the objective tumor response rate when compared to paclitaxel alone. The study did not show an effect on overall survival. The median PFS time was 11.3 months for the bevacizumab and paclitaxel arm and 5.8 months for the paclitaxel arm (HR= 0.48, $p < 0.0001$). It is noted that the magnitude of the treatment effect on PFS is uncertain given the significant amount of missing data as detailed in our review (Section 6). Exploratory analysis taking into consideration the missing data provided a HR of 0.57. Confirmation of clinical benefit may be based on an analysis of the ongoing phase 3 studies.

Supportive data from AVF2119g study shows that bevacizumab in combination with capecitabine for 2nd and 3rd line treatment of patients with metastatic breast cancer had no effect on PFS and overall survival.

1.2 Risk Benefit Assessment

In E2100, data collection was limited to NCI-CTC grade 3-5 adverse events. A 20% increase in grade 3-5 toxicity was observed in the bevacizumab plus paclitaxel arm. Severe and life-threatening adverse events occurring more frequently in patients receiving bevacizumab and paclitaxel were sensory neuropathy (24.2% vs. 17.5%), hypertension (16.0% vs. 1.4%), fatigue (10.7% vs. 5.2%), infection without neutropenia (9.1% vs. 4.6%), neutropenia (5.8% vs. 3.2%), vomiting (5.5% vs. 2.3%), diarrhea (4.7% vs. 1.4%), bone pain (3.9% vs. 1.7%), headache (3.6% vs. 0.6%), proteinuria (3.0% vs. 0%), cerebrovascular ischemia (2.5% vs. 0%).

Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin. Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal pain/weakness/hypotension (2).

The most serious, and sometimes fatal, bevacizumab toxicities are gastrointestinal perforation, wound healing complications, hemorrhage, arterial thromboembolic events, hypertensive crisis, nephrotic syndrome, congestive heart failure, and neutropenic sepsis. The most common adverse events in patients receiving bevacizumab are asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

Bevacizumab is currently marketed in the United States for use in combination with oxaliplatin and 5-fluorouracil (5-FU)-based chemotherapy for first- (2004) and second line (2006) treatment of patients with metastatic colorectal carcinoma and for use in combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable or metastatic non-squamous histology, non-small cell lung cancer (2006).

The serious adverse events and deaths reported in the E2100 study are consistent with the known bevacizumab associated toxicity and no additional safety signals were reported.

It should be noted that the suboptimal safety data collection in study E2100 (Section 7) precluded a thorough assessment of the safety of bevacizumab in combination with paclitaxel in breast cancer patients.

1.3 Recommendation on Phase 4 Studies and/or Risk Management Steps

The following are Phase 4 Commitments under 21 CFR601.41 Subpart E, as a condition for accelerated approval Avastin for breast cancer.

Completion, analysis, study reports and primary datasets on the following two ongoing studies are required as demonstration of “due diligence” in the evaluation of potential clinical benefit from Avastin treatment for breast cancer:

- **Study BO17708**, “A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Docetaxel in Comparison with Docetaxel Plus Placebo as First-Line Treatment for Patients with HER2-Negative Metastatic Breast Cancer”
- **Study AVF3694g** “A Multicenter, Phase 3, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer.”

1.4 Recommendations for other Post Marketing Study Commitments

Additional post-marketing commitments agreed upon by FDA and Genentech Inc, are:

- To submit a clinical study report, including datasets, for study AVF3693g, “A Phase 3, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Treated Metastatic Breast Cancer.”
- To submit a clinical study report, including datasets, for study BO20231, “A Randomized, Open-Label, 2-Arm, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Trastuzumab/Docetaxel Compared with Trastuzumab/Docetaxel Alone as First Line Treatment for Patients with HER2 Positive Locally Recurrent or Metastatic Cancer.”
- To submit a clinical study report, including datasets, for study CALGB 40503, “A Endocrine Therapy in Combination with Anti-VEGF Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Endocrine Therapy Alone or Endocrine Therapy plus Bevacizumab for Women with Hormone-Receptor Positive Advanced Breast Cancer.”

2 Introduction and Regulatory Background

2.1 Product Information

Avastin® (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralization of the biologic activity of VEGF can result in the reduction of tumor vascularization and subsequent tumor growth.

2.2 Tables of Currently Available Treatments for Proposed Indication

The following table lists the agents approved by the FDA for use in metastatic breast cancer since 1953.

Table 1. Agents Approved by the FDA for use In Metastatic Breast Cancer

Indication	Agent	Year of Approval
Metastatic Breast Cancer	Methotrexate,	1953
	Cyclophosphamide	1959
	Thiotepa,	1959
	Vinblastine	1961
	5-fluorouracil	1962
	Doxorubicin	1974
2 nd and 3 rd line Metastatic Breast Cancer	Paclitaxel	1994
	Docetaxel	1996
	Trastuzumab	1998
	Capecitabine	1998
	Capecitabine + Docetaxel	2001
	Abraxane	2005
	Lapatinib	2006
	Ixabepilone	2007
1 st line Metastatic Breast Cancer	Trastuzumab +Paclitaxel	1998
	Gemcitabine + Paclitaxel	2004

Approvals for first line metastatic breast cancer, the proposed indication for this application, have been granted for trastuzumab plus paclitaxel (1998) and gemcitabine plus paclitaxel (2004).

Trastuzumab in combination with paclitaxel is approved for use in patients with metastatic breast cancer whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease. Regular approval was based on a statistically significant improvement in overall survival in patients who received trastuzumab plus chemotherapy.

Gemcitabine in combination with paclitaxel received regular approval in May, 2004, for 1st line treatment of patients with metastatic breast cancer based on an interim analysis showing strong trend toward overall survival effect in the gemcitabine arm (hazard ratio 0.823, stratified log rank p = 0.0489). This trend toward an OS effect, supported by the superiority of the gemcitabine/paclitaxel arm in time to documented tumor progression and objective tumor response rate along with good objective tumor response rates in the single arm phase 2 studies, was sufficient for regular approval of the sNDA.

2.3 Availability of Proposed Active Ingredient in the United States

Bevacizumab is marketed in the United States for use in combination with oxaliplatin and 5-fluorouracil (5-FU)-based chemotherapy for first- (2004) and second line (2006) treatment of patients with metastatic colorectal carcinoma and for use in combination with

carboplatin and paclitaxel for first-line treatment of patients with unresectable or metastatic non-squamous histology, non-small cell lung cancer (2006).

Since the initial marketing approval in February 2004, the Avastin package insert has been revised four times, to add safety information regarding: arterial thromboembolic events and infusion reactions (December 2004), gastrointestinal perforation (April 2006), reversible posterior leukoencephalopathy syndrome (RPLS) and nasal septum perforation (September, 2006) and non-gastrointestinal fistula formation (October, 2007).

2.4 Important Safety Issues with Consideration to Related Drugs

Anti-angiogenic products such as bevacizumab and other anti-vascular endothelial growth factor (VEGF) products are known to be associated with the following class effect toxicities: impaired wound healing, bleeding/hemorrhage, hypertension, thromboembolic events, cerebrovascular ischemia, left ventricular dysfunction, myocardial infarction, gastrointestinal perforation, gastrointestinal and non-gastrointestinal fistula formation proteinuria and reversible posterior leukoencephalopathy syndrome (RPLS).

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

This supplemental BLA was first submitted on May 23, 2006 (STN 125081/91/0). After review of the information submitted, FDA determined that the submission was inadequate to support a final approval action. FDA issued a Complete Response (CR) letter on September 8, 2006. The key issues of the CR letter were:

- The data set was incomplete, without a data cut-off date for efficacy and safety. As per Genentech, data collection and data clean-up was still ongoing
- FDA reiterated the need for an independent radiology review of the progression events in at least a subset of patients, given the subjective nature of the PFS endpoint and the open-label design of the E2100 study
- The submission was incomplete in regards to documentation of patient eligibility, baseline tumor description, study violations, drug exposure, and treatment delays/discontinuation due to toxicity.

In subsequent meetings and correspondence with Genentech, agreement was reached regarding:

- Data cut off dates for efficacy and safety
- Genentech would submit a "cleaned" dataset
- Genentech would conduct an independent, blinded review of all patients enrolled in the E2100 study to verify the efficacy results

- The primary regulatory endpoint would be PFS adjudicated by and independent review facility (IRF)
- Genentech would submit the updated survival data.

This current submission (STN125085\91\18) addresses the issues listed in the FDA CR letter of September 8, 2006.

Additional significant regulatory activity pertinent to this application is further outlined below:

- | | |
|-----------------|---|
| July, 2000 | Genentech met with the FDA to discuss the design of study AVF2119g, a phase 3 trial of capecitabine +/- bevacizumab for 2nd and 3rd line therapy of patients with MBC. The study was intended to support the approval of Avastin. |
| September, 2000 | Protocol AVF2119g submitted to the FDA. The study was opened for accrual in November, 2000. |
| October 2001 | NCI submitted Study E2100, a phase 3 trial of paclitaxel +/- bevacizumab for 1st line therapy of patients with MBC. The study was not identified by NCI as a trial intended to support drug approval. E2100 opened for accrual in December 2001. |
| March, 2002 | Study AVF2119g completed patient accrual. Genentech met with FDA to discuss a BLA filing based on this trial. |
| May, 2002 | E2100 was identified by Genentech as an additional study intended to support drug approval. FDA provided comments to NCI and noted that that the SAP for the study was extremely deficient. Key issues: <ul style="list-style-type: none">• The primary efficacy endpoint and important secondary endpoints were not clearly defined and identified in the SAP.• The primary analysis method (s) for the primary efficacy endpoint and other important secondary endpoints were not described. |
| September, 2002 | Results of AVF2119g indicated that the study failed its primary endpoint of PFS. |
| October, 2002 | In a 2nd letter to NCI regarding E2100, FDA again expressed concerns, that the study had been identified by Genentech as a trial intended to support Avastin approval and yet, NCI had not request to meet with FDA to discuss the adequacy of the trial design and analysis plan prior to study activation.

The FDA asked NCI to provide additional clarification regarding the SAP. |

- FDA stated that it was crucial that the primary endpoints and statistical plan be adequate if the study is to serve as the basis for drug approval.
- May 2004 E2100 completed patient accrual.
- October 2004 Genentech submitted a revised SAP addressing FDA's previous letters to NCI and requested a meeting to discuss the adequacy of E2100 to support an Avastin label expansion.
- The FDA noted that E2100 may not be adequate to support licensure due to the non-blinded nature of the study and the lack of pre-specified, detailed and objective radiological and clinical parameters for determination of disease progression.
- FDA noted that in support of regular approval for the proposed indication, Genentech must provide overall survival data. In reviewing the results of E2100, data from AVF2119g, which failed to demonstrate efficacy, would also be considered. Genentech asked if PFS would be an adequate endpoint for full approval. FDA replied that it depends on the overall robustness and magnitude of PFS and the results of the survival data at the time of the PFS analysis.
- April, 2005 1st interim efficacy analysis by ECOG DMC: PFS was reported to be 6.1 months vs. 10.9 months in favor of the bevacizumab/paclitaxel arm (HR 0.49, log rank $p < 0.001$). Interim survival analysis was reported HR 0.67, log rank test $p=0.01$. The trial was stopped based on these findings. Results were made public on April 14, 2005 by Genentech and at the ASCO meeting (May 2005).
- September 2005 Pre-sBLA meeting: the FDA agreed that E2100 could form the basis of the primary efficacy evaluation to support a sBLA. Genentech asked if PFS would support a full approval. The FDA said no. The endpoint of PFS will support an accelerated approval. Genentech was asked to submit data on overall survival at the time of filing. Mature data concerning overall survival will be requested as a post-marketing commitment and will convert the sBLA from accelerated approval to full approval.
- May 2006 Genentech submitted Avastin BLA supplement (sBLA) for first-line metastatic breast cancer
- July 2006 FDA issued a Filing Deficiencies Letter on July 21, 2006 that identified potential review issues based on a preliminary evaluation of the application.

September 2006 Review of the information and data by FDA determined that the information and data submitted to support the sBLA were inadequate for an approval action. FDA issued a Complete Response Letter on September 8, 2006

November 2006 – July 2007

Agreement was reached regarding content and format of a sBLA re-submission. During this time, FDA met with Genentech and sent five letters containing comments regarding revised versions of the statistical analysis plan and IRF charter.

August 2007

Genentech submitted on August 23, 2007 their complete response (sBLA STN.125085/91/18) to amend the supplement.

2.5 Other Relevant Background Information

Avastin is approved world-wide for use in colorectal cancer and non-squamous, non-small cell lung cancer. Avastin is approved in the European Union for use in renal cell cancer and breast cancer.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

E2100 study was sponsored by the National Cancer Institute under IND 7921 and conducted by Eastern Cooperative Oncology Group (ECOG). Study monitoring and auditing were the responsibility of ECOG. All data management was conducted by ECOG except for the data management activities pertaining to the retrospectively independent review of radiographic image data, which was conducted at Genentech.

The overall organization of this sBLA re-submission is acceptable. Genentech addressed all issues listed in the Complete Response Letter of September 8, 2006. During the review process, additional information/clarification was requested thru multiple queries to Genentech in order to complete the review.

During the review process it was noted that case report forms (CRF) submitted with the application were incomplete in regards to the independent radiographic reading data. The submission did not include all reads performed by the Independent Review Facility (IRF), but only the read performed by “the definitive radiologist read”. In addition, it was found that the database regarding IRF reading had not been fully “cleaned”. Hence the FDA was unable to fully assess the accuracy of the independent radiologist results. Genentech was asked to submit a

“cleaned” database, as well as a complete set of CRF for all 722 patients. These were submitted on December 14, 2007.

Safety data collection for study E2100 was suboptimal (refer to Section 7.2), which precludes a thorough assessment of the safety of bevacizumab in combination with paclitaxel in breast cancer patients.

We did not agree with the causes of death on study attributions by Genentech (Section 7.3.1) in several instances. It appears that Genentech relied on tables/data submitted by ECOG and did not perform an internal quality check.

The deficiencies identified during the review process undermine our overall confidence in the data submitted to support regular approval for this application.

3.2 Compliance with Good Clinical Practices

Study E2100 was conducted in accordance with all Department of Health and Human Services, Office of Human Research Protection and FDA regulations regarding the conduct of human research. Study AVF2119g and AVF0776g were conducted in accordance with current FDA Good Clinical Practices (GCPs) and local ethical and legal requirements. Written Institutional Review Board review and approval of the protocol and informed consent document and all subsequent changes was required prior to randomization of patients in the study.

The participating cooperative groups audited their respective study sites using policies and procedures modeled after the NCI guidance document. An on-site audit is required for sites within 18 months after entry of the first patients on an NCI-sponsored cooperative Group trial and then at least once every 36 months.

At FDA’s request, Genentech obtained from NCI a Certification for Participating Sites in E2100 study. A review of the listing indicated that only one participating site Staten Island Medical Group in New York was referred to the Office of Human Research Protection due to concerns based on the audit conducted at that site. The reason(s) for concern was not provided. The membership of the principal investigator and site was reported to be terminated by the NCI due to lack of accrual and is currently not participation in trials conducted by the NCI-sponsored cooperative group clinical trials program. The site enrolled 1 patient in the E2100 study.

No audit was conducted by the Division of Scientific Investigators (DSI) for this application.

3.3 Financial Disclosures

Pivotal study E2100 was conducted by ECOG under the sponsorship of the NCI. NCI provided funding and Genentech provided the drug for the study. Hence, pursuant to 21 CFR 54.2(h),

both NCI and Genentech are considered “sponsors” for the purposes of Part 54 Financial Disclosure by clinical investigators.

NCI began collecting and tracking financial disclosure information in March, 2002 from each investigator registering with NCI as part of NCI’s investigator registration process using the NCI CTEP Disclosure Form. In response to the September 2006 letter, Genentech enlisted a 3rd party to coordinate the generation and review of Financial Disclosure information on behalf of NCI. Genentech also performed due diligence in the collection of financial disclosure information prior to March 2002.

A total of 662 investigators were listed as participants for E2100 study. The financial disclosure information was available for 655 investigators (98%). Twenty-seven investigators (4%) reported a possible conflict of interest; however, the nature of the conflict was not reported.

Per FDA’s request (Complete Response letter of September 2006), Genentech provided financial disclosure statement for the E2100 ECOG study administrative body and the ECOG Data Monitoring Committee members involved in E2100 data analysis.

E2100 Study Administrative body: twelve individuals were part of the E2100 study administration body. Three investigators reported receiving payment from Genentech and/or Roche since the initiation of the study (advisory board, speaking honoraria, research or consultation). Genentech was unable to obtain financial disclosure from two investigators.

ECOG Data Monitoring Committee members: sixteen members served on the ECOG DMC from 2001 thru 2006. Five members reported a possible conflict of interest for receiving significant payments (> \$25,000) for research, consultation and/or honoraria. One member reported compensation in which the value of the compensation could be affected by the study outcome.

Reviewer’s Comment: Four percent of investigators listed as participants reported a possible conflict of interest. Eight out of 26 investigators (30%) who provided financial disclosure in the E2100 study administration body and data monitoring committee reported financial conflict of interest for receiving payment from pharmaceutical companies. Two investigators did not return financial disclosure. The potential for bias of the study result by ECOG is unclear.

4 Significant Efficacy/Safety Issues Related to 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.

4.1 Chemistry Manufacturing and Controls

Not applicable for this application.

4.2 Clinical Microbiology

Not applicable for this application.

4.3 Preclinical Pharmacology/Toxicology

Not applicable for this application.

4.4 Clinical Pharmacology

Pharmacokinetic and pharmacodynamic studies were not conducted in the E2100 study. The pharmacokinetics of bevacizumab monotherapy was previously determined from pharmacokinetic studies included in the original BLA submission. This supplement included study AVF0776g, a phase II trial to evaluate the safety, efficacy and pharmacokinetics of Avastin as monotherapy in patients with relapsed metastatic breast cancer. Pharmacokinetic findings are summarized in section 5.3.2. A formal review of the pharmacokinetic data from this study was not conducted.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The claim of efficacy for this application is supported by a single Phase 3 study, E2100.

Clinical study report and safety dataset from a phase 3 study (AVF2119g) of bevacizumab with or without capecitabine and a phase 2 study (AVF0776g) of bevacizumab monotherapy for 2nd and 3rd line breast cancer provide additional efficacy and safety information.

Table 2. Clinical Studies

PHASE	STUDY	TITLE	N	SECTION
III	E2100 (Pivotal)	A Randomized Phase III Trial of Paclitaxel Versus Paclitaxel Plus Bevacizumab (rhuMAb VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer	722	6 and 7
III	AVF2119g	A Multicenter, Open-Label, Phase III, Randomized, Active-Controlled Trial Evaluating the Efficacy, Safety, and Pharmacokinetics of rhuMAb VEGF (Bevacizumab), In Combination with Capecitabine Chemotherapy, in Subjects with Previously Treated Metastatic Breast Cancer	462	5.3.2
II	AVF0776g	A Phase II, Open-Label, Multidose, Multicenter Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Recombinant Humanized Monoclonal Anti-VEGF Antibody (rhuMAb VEGF) as Monotherapy in Subjects with Relapsed Metastatic Breast Cancer	75	5.3.3

5.2 Review Strategy

The review consisted of analysis of efficacy and safety electronic datasets from study E2100 and safety data from AVF2119g study. Case Report forms, patient narratives and line listings were reviewed. Clinical study reports from all three studies were reviewed. Studies are reviewed individually and no pooled analysis was performed for this supplement.

5.3 Discussion of Individual Studies

5.3.1 E2100 (PIVOTAL) STUDY: REFER TO SECTIONS 6 and 7

5.3.2 AVF 2119 g STUDY

- **Study Title**
 A Multicenter, Open-Label, Phase III, Randomized, Active-Controlled Trial Evaluating the Efficacy, Safety, and Pharmacokinetics of rhuMAb VEGF (Bevacizumab), in Combination with Capecitabine Chemotherapy, in Subjects with Previously Treated Metastatic Breast Cancer

- **Study Design**

AVF2119g is a multicenter, open-label, phase 3, randomized study evaluating the efficacy, safety, and pharmacokinetics of bevacizumab (BEV), in combination with capecitabine (CAP) in patients with previously treated metastatic breast cancer.

The study consisted of two treatment periods:

Treatment Period 1 (TP1): eligible patients were randomized 1:1 to receive CAP alone (2500 mg/m² per day (creatinine clearance > 50 mL/min) or 1875 mg/m² per day (creatinine clearance 30-50 mL/min) daily for 2 weeks followed by a 1-week rest period (3-week cycle) or CAP (same dose schedule as arm 1) plus BEV (15 mg/kg every 3 weeks). Treatment was given for up to 35 cycles or unacceptable toxicity.

Treatment Period 2 (TP2): patients in the BEV arm were eligible to continue BEV therapy either alone or in combination with other chemotherapy regimens after disease progression.

Randomization was stratified by ECOG PS (0 or ≥ 1) and number of chemotherapy regimens for metastatic disease (0 or ≥ 1).

The primary endpoint of the study was progression free survival as determined by IRF assessment and safety. The secondary endpoints were objective response, overall survival, duration of objective response, and time to deterioration in QOL.

The study was conducted by Genentech Inc. in 96 study centers in the US from November 2000 to September 2002.

- **Patient Population**

Major eligibility criteria: histologically confirmed carcinoma of the breast with metastatic disease that is currently progression, prior administration of both an anthracycline and a taxane in either the adjuvant or metastatic setting, bi-dimensionally measurable disease, ECOG 0 or 1, patients known HER-2 positive are not eligible unless previously relapsed following Herceptin therapy. Patients with known rhuMab VEGF risk factors are ineligible, i.e., known CNS disease, non-healing wound, ulcer, bone fracture, significant cardiovascular disease, recent surgical procedure, use of full dose anticoagulation, bleeding diathesis, active infection, proteinuria (> 500mg/24 hr). Patients must not have significant co-morbid disease and adequate organ function: ANC ≥ 1500/μl, platelet count ≥ 75,000/μl, IRN ≤ 1.5, total bilirubin ≤ 1.5 x uln, AST or ALT ≤ 2.5 x uln (≥ 5 x uln if known metastatic disease in the liver), serum creatinine ≤ 2.0 mg/dL, Hb ≥ 9 gm/dL.

- **Study Population:**

Efficacy analysis is based on the intent-to treat population, defined as all subjects who were randomized to study treatment.

Safety analysis is based on the treated population, defined as all subjects who received any amount of bevacizumab or capecitabine.

- Patient disposition

The study enrolled 462 patients, 230 patients in the capecitabine alone arm and 232 patients in the capecitabine plus bevacizumab arm. Patient disposition per Genentech is shown in Table 2.

Of the 444 patients treated in TP1, 213 in the CAP arm discontinued therapy, 70.0% due to progressive disease, 11.7% due to adverse event; 229 patients in the BEV + CAP arm discontinued therapy, 81.0% due to progressive disease, 10.3% due to adverse event. Three patient in the CAP arm and 4 patients in the BEV + CAP arm were reported to have died on study.

A total of 94 patients in the BEV + CAP arm continued treatment in TP2. Disposition of these patients is shown in the following table.

Table 3. Patient Disposition

	CAP N =230 (%)	BEV + CAP N = 232 (%)
Not treated*	15 (6.5)	3 (1.3)
Treated TP1	215 (93.5)	229 (98.7)
Completed treatment	2 (0.9)	3 (1.3)
Discontinued treatment	213 (92.6)	226 (97.4)
Progressive disease	161 (70.0)	188 (81.0)
Adverse event	27 (11.7)	24 (10.3)
Death	3 (1.3)	4 (1.7)
Other	21 (9.1)	10 (4.3)
Treated TP2		94 (40.5)
Completed treatment		4 (1.7)
Discontinued treatment		90 (38.8)
Progressive disease	Not applicable	60 (25.9)
Adverse event		14 (6.0)
Death		2 (0.9)
Other		14 (6.1)

**Reasons for no treatment were either per physician's decision or patient's decision*

- Demographics, underlying disease and drug treatments

Randomization was in general well balanced between the two arms. Key demographic and tumor characteristics and prior cancer treatment is summarized in Table 4.

Table 4. Demographics, Tumor/Disease Characteristics and Prior Cancer Treatment

	CAP N =230	BEV + CAP N = 232
Demographics		
Female	100 %	100 %
Age (years, range)	52.3 (30-77)	51.1 (29-78)
Race: white/black	80.4%/10.9%	80.6%/12.9%
Disease/tumor characteristics		
ECOG 0 – 1	100%	99.5%
Post menopausal	80.9%	78.4%
≥ 3 disease site	50.4%	49.1%
Visceral disease	77.8%	73.7%
Histology: infiltrating ductal carcinoma	86.9%	85.8%
Time since primary diagnosis (years, range)	3.6 (0.4 – 27.8)	3.1 (0.4 – 30.2)
Positive ER/PR	53.1%/44.2%	46.6%/36.8%
Positive HER2 status	25.3%	27.3%
Prior Cancer Therapy		
≥ 1 chemo regimen for metastatic disease	83.9%	84.9%
Other prior therapies		
Surgery	99.6%	98.3%
Radiation	76.5%	75.0%
Hormonal	61.3%	54.3%
Trastuzumab	23.9%	25.0%
Myeloablative therapy	10.0%	9.1%

- **Efficacy outcome**

Primary Endpoint

The median progression free survival (PFS) determined by independent review (Table 5) was 4.2 months in the CAP arm and 4.9 months in the CAP+ BEV arm (log-rank p-value = 0.86, hazard ratio 0.98).

Table 5. Progression Free Survival (IRF/INV)

	CAP (N=230)	CAP + BEV (N=232)
Subjects with an event	126	146
Disease Progression	124	143
Death	2	3
Censored Subjects	104 (45)	86 (37)
Progression Free Survival (months)		
Median	4.17	4.86
95% CI	(3.71, 5.13)	(4.17, 5.52)
Stratified Analysis ^a		
Hazard Ratio ^b	-	0.98
95% CI	-	(0.77, 1.25)
p-value (log-rank)	-	0.857

^a Stratification^a ECOG PS (0, 1), chemotherapy for metastatic disease (yes, no)

^b Relative to capecitabine alone

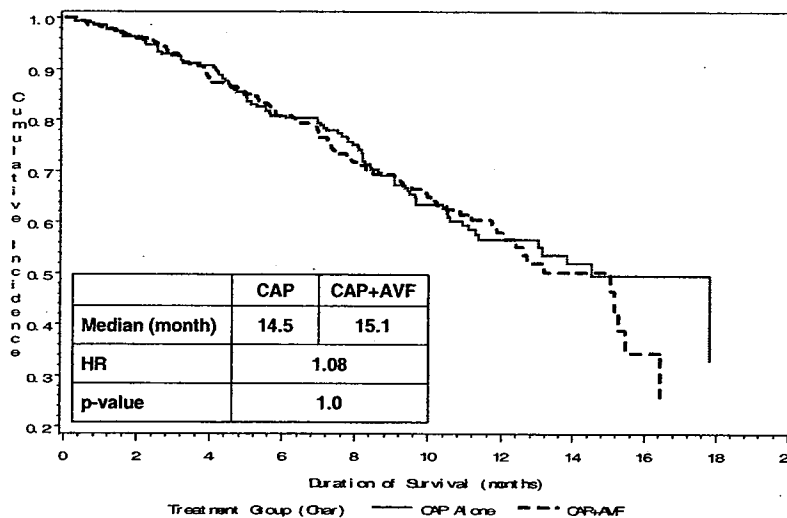
Adapted from Applicant's Table, AVF1129g, CSR, page 76 Table 12

Secondary Endpoints

Overall Survival

The median duration of survival (Figures 1) was 14.5 months in the capecitabine arm and 15.1 months in the capecitabine plus bevacizumab arm (log-rank p value = 0.63). The objective response rate was higher in the bevacizumab arm (19.8% vs. 9.1%).

Figure 1. Overall Survival



Objective Response

Objective response determined by an IRC is summarized in Table 6. The addition of bevacizumab to capecitabine improves objective tumor response (19.8% versus 9.1%); however bevacizumab responses were of short duration (4.96 months).

Table 6. Objective Tumor Response

	CAP (N=230)	CAP + BEV (N=232)
Overall Response Rate	21 (9.1)	46 (19.8)
Complete Response	0	0
Partial Response	21 (9.1)	46 (19.8)
Delta	10.7%	
95% CI	4.3%, 17.0%	
P- value	0.001	
Duration of Response	7.56 months	4.96 months

Patient-Reported Outcome

The primary measure of QOL in this study was time to deterioration in QOL by the Trial Outcome Index, Breast (TOI-B). The Sponsor claims that the addition of bevacizumab to capecitabine did not extend the time to deterioration in subjects' QOL nor contributed to a more rapid worsening of QOL compared to treatment with capecitabine alone.

- **Outcome of Safety Assessment**

The most common side effects observed in the AVF2119g trial are shown in Table 7. The most common adverse events reported in both treatment arms were asthenia, pain, diarrhea, nausea, vomiting and hand-foot syndrome, events known to be associated with capecitabine treatment. Events that occurred more frequently in the CAP+ BEV arm were headache (34.5%), hypertension (25.3%), epistaxis (16.2%) and albuminuria (22.7%).

Table 7. Most Common Adverse Events Reported in the AVF2119g trial

Adverse Event	CAP N=215 (%)		CAP + BEV N=229 (%)	
	Grade 3-4	All grades	Grade 3-4	All grades
Any adverse events	124 (57.7)	211 (98.1)	165 (72.1)	229 (100)
Body as a whole				
Asthenia	15 (7.0)	105 (48.8)	17 (7.4)	136 (59.4)
Headache	1 (0.5)	31 (14.4)	4 (1.7)	79 (34.5)
Pain	5 (2.3)	56 (26.0)	9 (3.9)	78 (34.1)
Cardiovascular - HTN	1 (0.5)	6 (2.8)	46 (20.1)	58 (25.3)
Digestive				
Diarrhea	24 (11.2)	113 (52.6)	27 (11.8)	132 (57.6)
Nausea	4 (1.9)	109 (50.7)	7 (3.1)	112 (48.9)
Vomiting	9 (4.2)	59 (27.4)	7 (3.1)	73 (31.9)
Stomatitis	1 (0.5)	41 (19.1)	4 (1.7)	59 (25.8)
Respiratory				
Dyspnea	11(5.1)	41 (19.1)	19 (8.3)	66 (28.8)
Epistaxis	0	3 (1.4)	0	37 (16.2)
Skin – Exfoliative dermatitis	52 (24.2)	162 (75.3)	66 (28.8)	193 (84.3)
Urogenital – Albuminuria	0	18 (8.4)	2 (0.9)	52 (22.7)

Serious Adverse Events

Adverse events known to be associated with bevacizumab are shown in Table 8. Bleeding events, hypertension and albuminuria occurred in more than 20 – 30% of the patients in the CAP+BEV arm. Grade 3-4 venous thrombosis was observed in 4.8 % of the patients. Grade 3 hypertension was reported in 20.1% of the patients in the CAP+BEV arm.

Table 8. Adverse Events Known to be Associated with Bevacizumab

Adverse Event	CAP N=215 (%)		CAP + BEV N=229 (%)	
	Grade 3-4	All grades	Grade 3-4	All grades
Any Thromboembolic Event	8 (3.7)	13 (6.0)	14 (6.1)	18 (7.9)
Pulmonary embolus	3 (1.4)	3 (1.4)	4 (1.7)	4 (1.7)
Venous thrombosis	4 (1.9)	9 (4.2)	11 (4.8)	17 (7.4)
Arterial thrombosis				
Cerebral ischemia	1 (0.5)	1 (0.5)	0	0
Left ventricle	0	0	1 (0.4)	1 (0.4)
Bleeding	1 (0.5)	26 (12.2)	1 (0.4)	68 (29.7)
Hypertension	1 (0.5)	6 (2.8)	46 (20.1)	58 (25.3)
Albuminuria	0	18 (8.4)	2 (0.9)	52 (22.7)
CHF/LVF/Cardiomyopathy	2 (1.0)	2 (1.0)	8 (3.5)	9 (3.9)

There were no incidences of cerebrovascular ischemia, myocardial infarction or gastrointestinal perforation reported in the AVF2119g study.

Deaths on AVF2119g Study

A total of 344 patients died by the study data cut off date (166 in CAP arm and 178 in the CAP+BEV arm). Death was attributed to progressive metastatic breast cancer in 71.6% (CAP arm) and 72.5% (CAP+BEV arm) of the patients.

Thirty three patients died during the study period (23 in TP1 and 10 in TP2). In CAP alone arm, 10/12 patients died due to disease progression and 2 due to adverse event (cardiopulmonary arrest of an unknown cause and possible pulmonary embolus) In the CAP+BEV arm, death was attributed to progressive disease in 20 patients (TP1 and TP2) and adverse event in one patient during TP-1 (neutropenia, sepsis)

The FDA agrees with the death attribution of these patients upon review of the data provided by the Genentech (data sets and selected narratives).

- **Discussion of findings/Conclusions**

AVF2119g failed its primary endpoint of progression free survival. Bevacizumab did not affect overall survival in this study. An increase objective response was observed but of short duration. The addition of bevacizumab to paclitaxel resulted in a 14.4% increase in grade 3-4 toxicity, mainly due to hypertension, thromboembolism and other adverse events know to be associated with bevacizumab. The most common adverse events reported in both treatment arms were events known to be associated with capecitabine treatment. No additional safety signals of concern were observed in the study.

5.3.3 AVF0776g STUDY

Study Summary:

AVF0766g is a phase 1/2, single arm study to evaluate the safety, efficacy, and pharmacokinetics of bevacizumab as monotherapy in patients with relapsed metastatic breast cancer.

The study was conducted in 2 centers in US from November, 1998 thru October, 2000. The study enrolled 75 patients. Patients received bevacizumab at 3 mg/kg (N=18), 10 mg/kg (N=41) or 20 mg/kg (N=16) every 2 weeks.

Grade 3 and Grade 4 adverse events were reported in 41% and 17% of the patients respectively. The most common AEs were hypertension, dyspnea, asthenia and headache. Hypertension was reported in 23% of the patients, with one patient experiencing grade 4 hypertensive encephalopathy. Venous thromboembolic event was reported in 3 patients. Proteinuria occurred in 7 patients, nephrotic syndrome was reported in 2 patients in this study. One patient

experienced congestive heart failure. Four patients discontinued study due to an adverse event: hypertensive encephalopathy, 2 nephrotic syndrome and one due to headache associated with nausea and vomiting. There were no deaths attributed to bevacizumab in this study.

Objective response was observed in one patient at 3 mg/kg, three patients at 10 mg/kg and 1 at the 20 mg/kg dose group (5/75, 6.7%).

Serum for pharmacokinetic analysis was available in 74 patients. The PK of Avastin appeared to be linear when administered at dose levels of 3, 10, or 10 mg/kg every 2 weeks, which is consistent with results from previous clinical trials.

6 Review of Efficacy

6.1 Proposed Indication

Bevacizumab is approved by the U.S. Food and Drug Administration (FDA) for use in first-line (2004) and second-line (2006) treatment of patients with metastatic colorectal cancer in combination with intravenous (IV) 5-fluorouracil (5-FU)-based chemotherapy. Bevacizumab is also approved for use in combination with carboplatin and paclitaxel in 1st-line treatment of patients with unresectable or metastatic non-squamous, non-small cell lung cancer (2006).

Genentech proposes to add the following indication to the current label: Avastin, in combination with paclitaxel, is indicated for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer.

6.1.1 Methods/Study Design

Study E2100 is an open-label, phase III, multicenter, randomized, controlled trial of patients who had not previously received chemotherapy for their locally recurrent or metastatic breast cancer. Eligible patients were randomized 1:1 to receive either:

- **Arm A** Paclitaxel 90mg/m² iv over 1 hr every wk for 3 wks followed by 1 wk rest
Bevacizumab 10 mg/kg following paclitaxel on wks 1 and 3 of every cycle
- **Arm B** Paclitaxel 90mg/m² iv over 1 hr every wk for 3 wks followed by 1 wk rest

Randomization was stratified according to disease-free interval (≤ 24 , > 24 months), number of metastatic sites (<3 , ≥ 3), prior adjuvant chemotherapy (yes, no) and ER status (positive, negative, and unknown).

Treatment was given every 4 weeks until disease progression, unacceptable toxicity, or death due to any cause (amendment 6 of the protocol removed the restriction of a maximum of 18 cycles). Cross over was not allowed.

Study Population

Patients with histologically or cytologically confirmed, HER2 negative, adenocarcinoma of the breast with measurable or non-measurable, locally recurrent or metastatic disease were eligible. Patients must not have received chemotherapy for locally recurrent or metastatic breast cancer.

Eligibility Criteria:

- Patients must have histologically or cytologically confirmed adenocarcinoma of the breast with measurable or non-measurable locally recurrent or metastatic disease. Locally recurrent disease must not be amenable to resection with curative intent.
 - Patients with HER-2 (gene amplification by FISH or 3+ overexpression by immunohistochemistry) are not eligible unless they have received prior therapy with Herceptin
 - Patients with unknown HER-2 status are not eligible unless Herceptin would be inappropriate or not indicated
- No history or radiologic evidence of CNS metastasis. No history of seizure or CVA.
- No prior chemotherapy for locally recurrent or metastatic breast cancer. Prior hormonal therapy is allowed, but this must have been discontinued at least 3 weeks prior to study entry.
 - No adjuvant or neoadjuvant taxane therapy within 12 months prior to randomization.
 - Any adjuvant chemotherapy regimen must be discontinued at least 3 weeks prior to study entry
- No major surgical procedure within 4 weeks prior to randomization
- No radiation within 3 weeks prior to study entry. Previously radiated areas must not be the only site of disease
- No history of bleeding diathesis or have used anticoagulant therapy within 10 days of study entry
 - No history of deep vein thrombosis or pulmonary embolism
 - No use of aspirin (>325 mg/day) or other non-steroidal anti-inflammatory medications within 10 days prior to randomization. Patients using dipyridamole, ticlopidine, clopidogrel and cilostazol (drugs known to inhibit platelet function) are not eligible
- ECOG performance status of 0 or 1
- Adequate organ function:
 - Absolute neutrophil count $\geq 1500/\text{mm}^3$ and platelet count $\geq 100,000/\text{mm}^3$
 - Total bilirubin $\leq 1.5 \text{ mg/dL}$ and SGOT $\leq 2 \times \text{uln}$ ($\leq 5 \times \text{normal}$ in patients with known liver involvement)
 - Creatinine $\leq 2.0 \text{ mg/dL}$
 - PTT and either IRN or PT $\leq 1.5 \times \text{normal}$

- Urine analysis by dipstick or complete analysis negative for protein. If $\geq 1+$ proteinuria, a 24-hour urine collection verifying < 500 mg proteinuria within 24 hours is required to confirm eligibility
- No clinically significant cardiovascular disease including myocardial infarction (within 12 months prior to randomization), unstable angina, grade 2 or greater peripheral vascular disease, uncontrolled congestive heart failure or uncontrolled hypertension (SBP > 170 , DBP > 95)
- No non-healing wound or fracture
- No hypersensitivity to paclitaxel or drugs using Cremophor, Chinese hamster ovary cell products or other recombinant human antibodies
- Age ≥ 18 years
- Women must not be pregnant or breastfeeding
- Women of childbearing potential and sexually active males must use an accepted and effective non-hormonal method of contraception
- No active infection requiring parenteral antibiotics

Study Endpoints

- **Primary endpoint:** progression free survival adjudicated by a blinded independent committee of radiologists and oncologists.
- **Secondary endpoints:** overall survival, response rate, duration of response and quality of life as assessed by FACT-B questionnaire.

Definition of Disease Progression

Per agreement with Genentech (FDA meeting of November 2, 2006), all tumor assessment data including pertinent clinical information were to be retrospectively reviewed by a blinded, independent review committee.

PFS is defined to be the time from randomization to disease progression as determined by the IRF, or death within 84 days of the last study treatment. The following censoring rules were applied:

1. If no PD or death by 2/9/05, censored at the date of last tumor assessment before the cutoff date
2. Dead before 2/9/05, but after 84 days following last treatment, censored at the last tumor evaluation date
3. If NTP prior to documented PD, censored at the time of last tumor assessment prior NTP
4. If no scans or clinical info submitted to IRF, censored at the randomization.

Efficacy Assessments

- Tumor assessment by scans or x-ray was performed at baseline, every 3 cycles, at the time off treatment and follow up.

- The specific radiographic modality was not mandated by the protocol beyond “scans and X-rays”
- All patients were to be followed for response until progressive disease, regardless if study therapy was discontinued prior to disease progression, and for survival for 5 years from the date of randomization.
- Patients who discontinued protocol therapy were to be assessed for tumor progression and non-protocol cancer therapy until disease progression and toxicity every 3 months for up to 2 years from randomization and every 6 months from 2 to 5 years from randomization.

Safety Assessments

- Adverse events were collected from three different sources: E2100 Toxicity Form (or NCI EPP, Expanded Participation Project form), the AdEERS database, and MedWatch data from ECOG.
- Adverse events were collected every 3 cycles (12 weeks) for patients on protocol therapy. The date of onset and resolution of the event was not collected. Following discontinuation of protocol therapy, adverse events were collected every 3 months up to 2 years after randomization and every 6 months, up to 5 years from randomization.
- Only grade 3-5 non-hematologic AEs and grade 4-5 hematologic AEs be reported for non-EPP patients for both treatment arms, regardless of attribution. For EPP patients, only adverse events considered possibly related to protocol therapy were reported.
- AdEERS collected only serious events from the bevacizumab and paclitaxel arm.

Statistical Analysis Plan

The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all patients who were randomized to protocol therapy.

The primary endpoint was PFS based on IRF assessment. A total of 546 PFS events were needed to provide 85% power to detect a 33 % increase in median PFS from 6 months in Arm B to 8 months in Arm A with a one-sided Type I error rate of 0.025. Two interim analyses for efficacy were planned in the protocol at 270 and 425 events using O'Brien-Fleming boundary for the adjustment of Type I error rate.

Secondary endpoints included OS, objective response rate, duration of objective response, and QOL. A final analysis for OS was planned after 481 deaths have occurred, which provides 80% power to detect a 29% improvement in median OS from 24 months to 31 months with a one-sided Type I error rate of 0.025. OS was analyzed the same way as that for PFS.

On May 2006, Genentech submitted the sBLA after the first interim analysis for efficacy. At that time ECOG concluded that the results were statistically significant. The submission was deemed inadequate (refer to Regulatory Background section above). Per agreement with FDA, the data cut off date for the sBLA submission was February 9, 2005, the date of the ECOG

interim analysis that led to stopping the trial. The overall survival cutoff date was October 21, 2006, the date at which the 481 death occurred. This was the number of events that constituted the full information required for the analysis of overall survival as stated in the primary SAP.

Protocol Amendments:

The original E2100 protocol was not archived at ECOG and a copy was not available for review. The study underwent 10 subsequent revisions; the vast majority consisted of administrative changes and safety updates regarding bevacizumab adverse events. Significant changes are summarized below:

Amendment 1 (December 31, 2002)

- Protocol objective was modified to include “time to progression”
- Secondary endpoints are clarified to state: as further secondary endpoints, the time from randomization to disease progression (TTP) and the duration of response will also be compared between the two arms)

Amendment 2 (January 29, 2003)

- Adverse event reporting requirements updated

Amendment 3 (July 3, 2003)

- Adverse event information regarding bevacizumab updated.

Amendment 4 (August 28, 2003)

- Revised plan for the evaluation of primary endpoint TTP, in patients who have entered without measurable disease
- Adverse event information regarding bevacizumab updated.

Amendment 5 (December 30, 2003)

- Adverse event information regarding bevacizumab updated
- Administrative changes

Amendment 6 (March 9, 2004)

- Treatment duration changed from a maximum of 18 cycles to a continuation of treatment until disease progression or unacceptable toxicity.

Amendment 7 (February 23, 2005)

- Adverse event information regarding bevacizumab updated

Amendment 8 (August 23, 2005)

- Adverse event information regarding bevacizumab updated

Amendment 9 (February 22, 2006)

- Administrative update

Amendment 10 (May 2 and May 30, 2007)

- Administrative updates

6.1.2 Conduct of the Trial

Eligibility: 6.8% (49/722) were determined to be ineligible for the study by ECOG, 24/49 had scans performed > 4 weeks prior to randomization and 14/49 due to failure to discontinue prior hormonal or radiation therapy > 3 weeks prior to start of therapy.

Protocol deviation: Protocol deviations as per ECOG and Genentech are shown in Table 9. Approximately 30% of the patients had one significant protocol deviation by either ECOG or Genentech. An ECOG case evaluation form to verify protocol deviation was unavailable in 33/722 patients. The most significant deviations were continuing treatment beyond progression (6.0 %). Stratification errors could not be fully verified, due to lack of documentation by ECOG. Stratification error for ER status and prior adjuvant chemotherapy was reported in 7% of the patients.

A total of 113 (15.7%) patients initiated a non-protocol anti-cancer therapy (NPT) prior to documented disease progression (58 in PAC arm, 55 in PAC/BEV arm). Reason for initiation of another protocol was not captured in the case report form. Sixty patients (8.3%) initiated a non-protocol chemotherapy, 47 (6.5%) received hormonal therapy and 15 patients (2.1%) received radiation therapy. For the definition of PFS, these patients were censored at the time of the last tumor assessment, prior to initiation of NPT.

Table 9. Significant Protocol Deviations

Protocol Deviation by ECOG and Genentech	PAC N=354 (%)	PAC/BV N=368(%)	Total N=722(%)
Available ECOG form to verify protocol deviation	340	349	689
Numbers with deviation per ECOG	25 (7.4)	39 (11.2)	64 (9.3)
• Treated beyond progression	15 (4.4)	26 (7.4)	41 (6.0)
• Incorrect treatment arm given	1 (0.3)	2 (0.6)	3 (0.4)
• Others	10 (2.9)	12 (3.4)	22 (3.2)
Number with deviation per Genentech	83 (23)	82 (22.2)	165 (22.8)
• Stratification errors* (ER status and adj. chemo)	24 (6.8)	27 (7.3)	51 (7.1)
• No evidence of disease at enrollment	1 (0.3)	0	1 (0.3)
• Initiation of Non-Protocol anti-cancer therapy prior to documented PD	58 (16.4)	55 (14.9)	113 (15.7)
- Chemotherapy	33 (9.3)	27 (7.3)	60 (8.3)
- Hormonal Therapy	25 (7.1)	22 (6.0)	47 (6.5)
- Radiation Therapy	5 (1.4)	10 (2.7)	15 (2.1)
Other	3 (0.9)	3 (0.8)	6 (1.5)

* Unable to fully assess stratification errors due to lack of documentation.

6.1.3 Demographics

Study Period: December 21, 2001 – December 30, 2005
Data cutoff dates: Efficacy – February 9, 2005
Overall survival – October 21, 2006
Safety – August 9, 2005 (October 30, 2006 for NCI AdEERS)
Cause of death – no cutoff; events in database as of June 6, 2007

A total of 258 centers from the following cancer cooperative groups participated in the study: ECOG, CALGB, SWOG, NSABP, NCCTG, RTOG, GOG and EPP, NCI's Expanded Participation Project. A total of 722 patients were enrolled, with 663 (91.8%) patients enrolled in USA sites and 59 patients (8.2%) enrolled in non-USA sites.

Enrollment per center: 1 to 37 patients

Sites that enrolled most patients:

- University of Pretoria, South Africa – 37
- Instituto Nacional de Enfermedades Neoplasicas, Peru – 22
- US- Rush University Medical Center, Illinois – 23
- Indiana University Medical Center 18
- Johns Hopkins University, MD – 15

A total of 722 patients were randomized to the study. Patient characteristics of the ITT population are shown in Tables 10. Randomization was in general well balanced, with the exception of presence of measurable disease at baseline (77.1% in the paclitaxel arm versus 68.5% in the paclitaxel plus bevacizumab arm).

The median age was 55 years old (range 27 to 85), 55% of the patients were post menopausal, 98.3 % of the patients had metastatic disease and 45.7% of the patients had disease involving more than 3 sites. The most common sites of involvement were bone, liver and lung; 61.8 % of the patients were ER positive.

Table 10. Patient Demographics, Tumor Characteristics and Prior Therapy

	PAC N = 354	PAC + BEV N = 368	TOTAL (N=722)
Demographics			
Gender: Female	350 (98.9)	366 (99.5)	716 (99.2)
Age: median (range)	55 (27-85)	56 (29-84)	55 (27-85)
Race white	266 (75)	284 (77.2)	550 (76.2)
black	35 (9.9)	34 (9.2)	69 (9.6)
others	30 (8.5)	26 (7.1)	56 (7.8)
Menopausal status			
Pre	55 (15.5)	63 (17.1)	118 (16.3)
Post	204 (57.6)	195 (53.0)	399 (55.3)
Tumor Characteristics			
Metastatic	349 (98.9)	360 (97.8)	709 (98.3)
Locally recurrent	4 (1.1)	8 (2.2)	12 (1.7)
No. of involved sites			
< 3	184 (52)	208 (56.5)	392 (54.3)
≥ 3	170 (48)	160 (43.5)	330 (45.7)
Most common sites of involvement			
Bone	192 (54.4)	201 (54.6)	393 (54.5)
Liver	157 (44.5)	144 (39.1)	301 (41.7)
Lung	146 (41.4)	153 (41.6)	299 (41.5)
Local-regional	116 (32.9)	121 (32.9)	237 (32.9)
Distant nodes	97 (27.5)	103 (28.0)	299 (27.7)
Bone only	27 (7.6)	36 (9.8)	63 (8.7)
ER status			
Positive	127 (35.9)	138 (37.5)	265 (36.7)
Negative	233 (63.0)	223 (60.6)	446 (61.8)
Unknown	4 (1.1%)	7 (1.9)	11 (1.5)
HER2 status (FISH/IHC)			
Negative	316 (89.3)	334 (90.8)	650 (90)
Positive	6 (1.7)	9 (2.4)	15 (2.1)
Unknown	32 (9.0)	25 (6.8)	57 (7.9)
Disease-free interval			
≤ 24 months	146 (41.2)	150 (40.8)	296 (41.0)
> 24 months	208 (58.8)	218 (59.2)	426 (59.0)
Measurable disease at baseline			
Yes	273 (77.1)	252 (68.5)	525 (72.7)
No	81 (22.9)	116 (31.5)	197 (27.3)

In regards to prior breast cancer treatment (Table 11), the majority of the patients (60.8 %) received prior hormonal therapy, either in the adjuvant or metastatic setting. The majority of the patients (65.8%) had received adjuvant chemotherapy; 50.4% of the patients had received an anthracycline and 19.7% had received a taxane. The distribution of the patients was balanced between arms regarding the prior cancer treatment modality.

Table 11. Prior Cancer Treatment

Prior Cancer Treatment	PAC (N=354)	PAC/BV (N=368)	Total (N=722)
Hormonal therapy			
Adjuvant	175 (49.4)	168 (45.7)	343 (47.5)
Metastatic	128 (36.2)	134 (36.4)	282 (36.3)
Chemotherapy			
Adjuvant	231 (65.3)	244 (66.3)	475 (65.8)
Metastatic	1 (0.3)	1 (0.3)	2 (0.3)
Prior taxane	68 (19.2)	74 (20.1)	142 (19.7)
Prior anthracycline	180 (50.8)	184 (50.0)	364 (50.4)

6.1.4 Patient Disposition

A total of 722 patients were randomized in a 1:1 ratio to paclitaxel alone (354 patients) or paclitaxel + bevacizumab (368 patients). Patient disposition and reason for treatment discontinuation based on all data contained in the ECOG database as of the safety data cutoff of 9 August 2005 are shown in Table 12. Of the 711 treated patients, 664 patients (92.0%) had discontinued protocol therapy.

Table 12. Patient Disposition and Reason for Protocol Therapy Discontinuation
 Based on ECOG CRF (cutoff date of 9 August 2005)

Status/Reason for Discontinuation	PAC	PAC/BEV	Total
	N = 354 (%)	N = 368 (%)	N = 722 (%)
Treated	346 (97.7)	365 (99.2)	711 (98.5)
Not known to have discontinued protocol therapy	8 (2.3)	39 (10.6)	47 (6.5)
Discontinued protocol therapy	338 (95.5)	326 (88.6)	664 (92.0)
Treatment completed per protocol	11 (3.1)	17 (4.6)	28 (3.9)
Disease progression/relapse during active treatment	193 (54.5)	167 (45.4)	360 (49.9)
Toxicity/side effects/complications	68 (19.2)	74 (20.1)	142 (19.7)
Death on study	5 (1.4)	6 (1.6)	11 (1.5)
Patient withdrawal or refusal	30 (8.5)	27 (7.3)	57 (7.9)
Alternative therapy	6 (1.7)	8 (2.2)	14 (1.9)
Other complicating disease	1 (0.3)	4 (1.1)	5 (0.7)
Other*	24 (6.8)	23 (6.3)	47 (6.5)
Not treated	8 (2.3)	2 (0.5)	10 (1.4)
Patient not eligible	1 (0.3)	1 (0.3)	2 (0.3)
Patient refused treatment	2 (0.6)	0 (0.0)	2 (0.3)
Disease progression before active treatment	1 (0.3)	0 (0.0)	1 (0.1)
Other	4 (1.1)	1 (0.3)	5 (0.7)
Unknown	0 (0.0)	1 (0.3)	1 (0.1)

*"Other": include suspicion of progression, voluntary treatment break, or by the physician discretion.

6.1.5 Analysis of Primary Endpoint

Reviewer's comment: All efficacy analyses presented in the following section were conducted in collaboration with the Biometrics Division, Biologics and Therapeutics Statistical Staff, Hong Lu, PhD, Mathematical Statistician. All data mining and analyses were conducted by Dr. Lu. Please refer to Dr. Lu's review for additional statistical analysis.

Progression Free Survival (PFS)

Results of PFS based on IRF assessment is shown in Table 13. The median PFS time was 11.3 months for the PAC/BEV arm and 5.8 months for the PAC arm, (HR = 0.48, p < 0.0001). One hundred eighty four patients (52%) in the PAC arm and 173 patients (47%) in the PAC/BEV arm had an event. The Kaplan-Meier curves for PFS are displayed in Figure 2.

**Table 13. PFS Results based on IRF Assessments
 (data cut off date of Feb 9, 2005)**

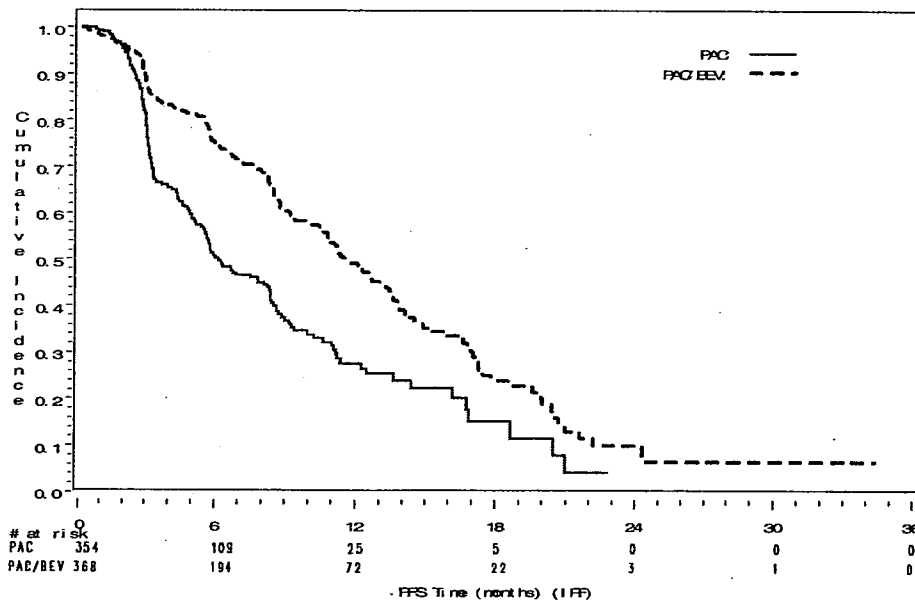
	PAC N=354 (%)	PAC/BEV N=368 (%)
Patients with an event (%)	184 (52.0)	173 (47.0)
Censored (%)	170 (48.0)	195 (53.0)
Earliest contributing event		
Disease Progression	166	158
On-Study death ^a	18	15
Median (month)	5.8	11.3
HR ^b 95% CI	0.48 (0.38, 0.61)	
p-value ^c	<0.0001	

^a Death within 84 days of the last protocol therapy

^b HR was estimated by the stratified Cox regression method. The strata were disease-free interval (≤ 24 , > 24 months), number of metastatic sites (< 3 , ≥ 3), adjuvant chemotherapy (yes, no), and ER status (positive, negative, or unknown).

^c p-value by the stratified Cox regression method

Figure 2. Progression-Free Survival



Exploratory Analysis

An exploratory analysis for PFS based on ECOG assessment was conducted. The median duration of PFS was 11.4 months for the PAC/BEV arm and 5.8 months for the PAC arm, (HR = 0.42, $p < 0.0001$). Two hundred and forty-four patients (68.9%) in the PAC arm and 201 patients (54.6%) in the PAC/BEV arm had an event.

FDA's Review of PFS as the Primary Efficacy Endpoint

This application rests solely on evidence of an improvement on PFS in a single study. A 5.5 month improvement in PFS is claimed by Genentech. In considering this claim, the FDA needs to verify the robustness of the claim (i.e., is there an effect?) and the magnitude of the effect (i.e., is the 5.5 month improvement claim reliable?).

1. Robustness of the PFS claim

To evaluate the robustness of the effects on PFS, the reviewers conducted a number of sensitivity analysis and review the objective responses of the study.

2. Magnitude of the effect

The optimal way to measure the magnitude of the treatment effect is to have a reliable way of identifying when it occurs and to be able to detect it instantaneously, as one does for death in an analysis of overall survival. Because disease progression is assessed intermittently (in E2100, every 12 weeks) and not continuously, there is always a degree of uncertainty in measuring this endpoint.

This uncertainty can be even greater if the assessment of progression does not occur at the protocol-specified assessment time point or if the assessment of progression can not be verified, as in the case of missing data, i.e., missing scans and lost to follow-up

To assess the magnitude of effect, we evaluated the reliability of detecting progressive disease based on radiographic studies. Specifically, we asked whether two individuals reviewing the same set of x-ray films could arrive at the same conclusion regarding whether disease progression occurred or not. Concordance/discordance rate and reason for discordance between the independent radiologists and between the independent radiologists (IRF) and the ECOG investigators were analyzed and presented below.

- **Missing Data**

- **Scan Availability to Independent Review Facility (IRF) for PFS Assessment**

The primary endpoint was Progression Free Survival (PFS) adjudicated by a blinded Independent Review Facility (IRF). Scans were retrospectively collected by Genentech and forwarded to the

IRF for determination of disease progression events and for objective tumor response assessment. Genentech was unable to collect scans for 10% of the study population.

The number and percent of patients with any scan available to the IRF are summarized in Table 14. In total, 73 patients (10.1%) did not have any radiographic images submitted to the IRF.

Table 14. Radiographic Scan Availability to IRF

	PAC N=354 (%)	PAC/BV N=368(%)	Total N=722(%)
Patients with scans submitted to IRF	319 (90.1)	330 (89.7)	649 (89.9)
Patients without scans submitted to IRF	35 (9.9)	38 (10.3)	73 (10.1)

The number of patients with missing radiographic images for the first year of study (from baseline to Cycle 12) is summarized in Table 15. In the PAC arm, the percent of missing radiographic images ranges from 4.2% to 11.8% among those patients who was expected to have a scan visit. In the PAC/BEV arm, the percent of missing radiographic images ranges from 3.0% to 8.8% among those patients who was expected to have a scan visit.

Table 15. Completely Missing Radiographic Images by Visit per IRF Randomized Patients with at Least One Scan Available to the IRF

Visit	PAC N=319 (%)		PAC/BEV N=330 (%)	
	Patients expected to have a radiographic assessment	Patients with completely missing radiographic images	Patients expected to have a radiographic assessment	Patients with completely missing radiographic images
Baseline	319	15 (4.7)	330	18 (5.5)
cycle 3	166	7 (4.2)	233	7 (3.0)
cycle 6	87	8 (9.2)	156	11 (7.1)
cycle 9	38	3 (7.9)	108	2 (1.9)
cycle 12	17	2 (11.8)	57	5 (8.8)

- Lost to follow up

A total of 247 (34%) of the patients were not followed until an IRF-determined PFS event or the end of study (no tumor assessments within 3 months of the data cutoff date February 9, 2005).

Among these 34% of patients lost to follow-up, 6% were due to no scans or pertinent clinical information, 11% were due to initiation of non-protocol anti-cancer therapy (NPT), 12% were due to censoring by IRF for those patients who were determined as PD by ECOG, and 5% were without a clear reason for lost-to-follow-up (Table 16). Although the first 29% of lost-to-follow-up (6%+11%+12%) may not reflect a poor quality study conduct, they do affect the confidence on the reliability of PFS results.

Table 16. Lost of Follow up

	ITT Population N = 722 (100%)
Reason for Lost to follow up	Lost to follow up N = 247 (34%)
No scans or pertinent clinical information	43 (6%)
Initiation of non-protocol anti-cancer therapy (NPT)	79 (11%)
Censoring by IRF for patients who were determined as PD by ECOG	87 (12%)
No clear reason	36 (5%)

Reviewers Comment: it should be noted that Genentech reported 37% of lost-to-follow-up in the Oncology Drug Advisory Committee meeting held on December 5, 2007. The difference between FDA and Genentech is explained by the factor that Genentech's result was based on the difference between the PFS event (or censoring) date and the data cutoff date. If the difference between the PFS date and the efficacy data cutoff date February 9, 2005 is longer than 3 months, then the patient was counted as a lost-to-follow-up. The difference of 3% between FDA and sponsor's results are due to the inclusion, by the sponsor, of those patients who took NPT 3 months before the data cutoff date (therefore, PFS was censored at the NPT use) but still had tumor assessment data within 3 months of data cutoff date as lost-to-follow-ups.

Sensitivity Analysis to Assess the Impact of Missing Value and Lost-to Follow-up on PFS

To assess the robustness of the magnitude of PFS result with the presence of missing value and lost-to-follow-up, several sensitivity analyses were conducted. Results are shown in Table 17.

Table 17. PFS Sensitivity Analysis to Assess the Impact of Missing Data

IRF-Assessed PFS Analysis	Hazard Ratio	(95% CI)
Primary analysis	0.48	(0.39, 0.61)
PFS analysis based on missing tumor assessments ^a	0.48	(0.39, 0.61)
PFS analysis with non-protocol therapy (NPT) use and early discontinuation as PD events ^b	0.50	(0.41, 0.59)
PFS analysis without censoring for anti-tumor NPT	0.57	0.46, 0.71)
PFS analysis including deaths observed after completion of tumor assessments ^c	0.48	0.38, 0.61)
PFS analysis including all deaths before 2/9/05 ^d	0.54	(0.44, 0.66)
Worse-case analysis ^e	0.78	(0.64, 0.95)

- a. Patients with a PD who missed the evaluation immediately prior to the PD had their PD date replaced by the date of the first missed tumor assessment.
- b. NPT and early discontinuation (no tumor evaluation within 168 days of data cutoff date) were considered PD events.
- c. Deaths within 84 days of last tumor assessment were considered.
- d. All death before 2/9/05 were considered.
- e. NPT and early discontinuation were considered PD events for patients in the PAC/BEV arm only.

Reviewers' Comment:

Various sensitivity analyses were conducted to assess the robustness of PFS results. The results of these sensitivity analyses are consistent with that of the primary analyses in general (HR 0.48 to 0.57), with exception of worse-case analysis, when NPT initiation and early discontinuation were considered PD events for patients in the paclitaxel and bevacizumab arm only (HR 0.78). Refer to statistical review by Dr. Hong Lu for additional sensitivity analyses.

- **Discordance in Radiographic Reads to Determine Disease Progression**
 - **Discordance between Independent Radiologists (IRF) in PFS Determination**

Two radiologists were assigned to review all available scans for each clinical trial subject in order to determine the presence and date of radiographic disease progression. These readings were performed independently and blinded to the treatment which the patient received.

If the results of the two readings were discordant, a third radiologist performed an additional reading to arrive at a final adjudicated interpretation of the radiology results. In addition, a medical oncologist reviewed clinical records and other information to make a determination of disease progression based on clinical, or non-radiological, criteria.

In order to assess the reliability of the radiologically-based, tumor-related endpoints, FDA evaluated the consistency between the two IRF radiologists in regarding the presence of disease progression and the data of progression.

There were a total of 649 patients for whom radiologic scans were provided to the IRF. Among these 649 patients, there were 295 patients (45.5%) where the two radiologists did not agree on the status of disease progression or of tumor response or in whom they identified a different date for disease progression or onset of response (Table 18). The discordance rates between the two radiologists were similar between the two treatment arms.

Table 18. Lack of Consistency between the IRF Radiologists in Scan Reading

	N	No. Patients Adjudicated for Discordant Response or PD Status/Date
Patients with Scan	649	295 (45.5%)
PAC	319	138 (43.3%)
PAC/BEV	330	157 (47.6%)

This reviewer also conducted an assessment of the lack of consistency with regard to the two IRF radiologists for disease progression events. Among the 649 patients with scans available for IRF review, there were 217 patients, which account for 33.4% of the study population where the two radiologists reached different conclusions regarding disease progression status or date of disease progression. The level of disagreement on disease status or date of disease progression was higher among patients with a final IRF-determination of disease progression. Among the 278 patients with a final IRF-determination of disease progression, the two radiologists did not agree on the disease progression status or date of progression in 45.0%. Among the 371 patients that had no evidence of radiographic progression by the final IRF assessment, the two radiologists did not agree on disease progression status in 24.8% of these patients. These results are displayed in Table 19 below.

Table 19. Lack of Consistency between IRF Radiologists for PD Status or Date

	N	No. of Patients with Discordant PD Status or Date (%)
Patients with Scan	649	217 (33.4)
Radiographic PD	278	125 (45.0)
No Radiographic PD	371	92 (24.8)

Reviewers' Comment: FDA continues to gain experience regarding the reliability of radiologically-determined disease progression and at this time does not have sufficient experience to say whether the 33.4% rate of discordance between two radiologists is unusual.

However, the level of discordance suggests a lack of reliability in the measurement of a given patient's PFS, particularly for patients with disease progression events.

- Discordance between IRF radiologists and ECOG in PFS Determination

The discordance between IRF and ECOG determination of PFS status (event/ no event) was assessed. Results are shown in Table 20.

IRF disagreed with ECOG on PFS status or date of progression in a total of 368 patients (51%) evaluated. Of the 368 patients, IRF disagreed with ECOG in 174 patients regarding PFS status (progression, yes or no). In 194 patients IRF and ECOG agreed in PFS status (yes, progressed) but disagreed on the date of progression. The reasons and extend of progression date disagreement is further discussed below (page 41, Table 22).

Table 20. Lack of Consistency between IRF and ECOG for PFS Event Status or Date.

IRF and ECOG determination Disease Progression	ITT population N= 722
Disagreed in PFS Status	174 (24%)
• IRF is PD, ECOG is no PD	43 (6%)
• IRF is no PD ECOG is PD	131 (18%)
Agreed in PFS status but disagreed in PFS date	194 (27%)
TOTAL	368 (51%)

In looking at the direction of the disagreements, we consider whether the investigators consistently or generally favor the experimental arm over the control arm.

In Table 21, we provide the discordance rate between the IRF and ECOG investigators for disease progression status by treatment arm. In the first column, 3.4% of patients in the PAC arm and 8.4% patients in the PAC/BEV arm were determined to have disease progression by the IRF but no evidence of disease progression by ECOG investigators. Therefore, the discordance rates are slightly different for the two study arms, with the difference favoring the PAC/Bev arm over the PAC arm in ECOG investigator-determined assessment of PFS.

Table 21. Discordance between IRF and ECOG in PFS Event Status

Treatment Arm	No. of discordance (%)	
	IRF progressed ECOG censored	IRF censored ECOG progressed
PAC	12 (3.4)	72 (20.3)
PAC/BEV	31 (8.4)	59 (16.0)
Total	43 (6.0)	131 (18.1)

Extend of Disagreement in PD date between IRF and ECOG

To further analyze the concordance/discordance between the independent radiology and ECOG's review of the scans to determine progression, we looked into the reasons and the extent of discordance. Results are shown in the following table.

**Table 22. Reasons for Differences in PFS Dates
 (Patients with Event Status Agreed by ECOG and IRF with Difference in PFS Date)**

	TOTAL N = 194
Agreed upon PFS status is event	143 (73.3%)
Event is PD by both IRF and ECOG	125 (64.4%)
• Difference in PD dates < 6 weeks	39 (20.1%)
• Differences in PD dates ≥ 6 weeks	86 (44.3%)
Event is PD per IRF and death per ECOG	1 (0.5%)
Event is PD per ECOG and Death per IRF	17 (8.8%)
Agreed upon PFS status is censor	51 (26.3%)
• Difference in last tumor assessment dates < 6 weeks	15 (7.7%)
• Difference in last tumor assessment dates ≥ 6 weeks	36 (18.6%)

[^] Table adapted from Genentech's submission of 10/23/07, Table 1, page 7 in response to FDA's information request

The independent radiologists reviewers agreed with ECOG with PFS status is event, but did not agreed on the date of progression in 194 patients. IRF and ECOG agreed upon PFS is an event in 143 (73.3%) of the cases, however they differed in PD dates in 125 (64.4%) of the cases: in 20.1% the difference in PD date was < 6 weeks, in 44.3% of the cases, the difference in PD date determination was ≥ 6 weeks.

IR and ECOG agreed upon PFS status is censored in 51 (26.3%) of the cases: in 7.7% the difference in last tumor assessment dates was < 6 weeks. In 18.6% of the cases, the difference in last tumor assessment dates by ECOG and IRF was ≥ 6 weeks.

Reviewers Comment:

As discussed above, because disease progression is assessed intermittently and not continuously, there is always a degree of uncertainty in measuring this endpoint. To assess the magnitude of PFS effect claimed by Genentech, we evaluated the reliability of detecting progressive disease based on radiographic studies. We have found that IRF radiologist reading the same set of scans disagreed between themselves in 34% of the cases. IRF disagreed with ECOG investigators in 51% of the cases, furthermore, in 125 (64.4%) patients, IRF and ECOG disagreed on the date of progression. In 86 cases (44.3%) the disagreement on the progression date differed in ≥ 6 weeks.

These findings, in addition to the missing data and patients lost to follow up described above, further decrease our confidence in the magnitude of the PFS effect claimed by Genentech.

6.1.6 Analysis of Secondary Endpoints(s)

Overall Survival

The overall survival results are shown in Table 23. The cutoff date for overall survival analysis was October 21, 2005 when a total of 481 deaths had occurred (238 (67.2%) in the PAC arm and 243 (66.0%) in the PAC/BEV arm). There was no statistically significant difference in the median OS PAC/BEV arm (26.5 months) compared to the PAC arm (24.8 months) with $p=0.1374$. The hazard ratio was 0.87. The Kaplan-Meier curves for OS are displayed in Figure 2.

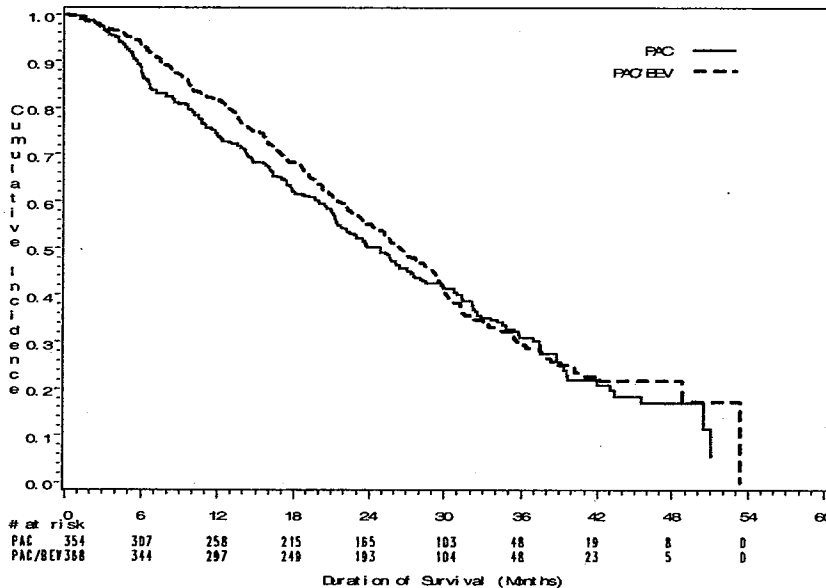
Table 23. Overall Survival

	PAC (N=354)	PAC/BEV (N=368)
No. of patients who died ^a (%)	238 (67.2%)	243 (66.0%)
Median (moth)	24.8	26.5
HR ^b (relative to PAC)	0.869	
95% CI ^b	(0.722, 1.046)	
p-value ^b	0.1374	

a: Cutoff date October 21, 2005

b: Analyses by the stratified Cox method. The factors are disease-free interval (≤ 24 , > 24 months), number of metastatic sites (< 3 , ≥ 3), adjuvant chemotherapy (yes, no), and ER status (positive, negative, or unknown)

Figure 2. Overall Survival



Objective Tumor Response

Tumor response was assessed by RECIST. IRF assessed objective tumor response in patients with measurable disease is shown in Table 24. Overall response rate was significantly higher in the PAC/BEV arm when compare to PAC alone (48.9 % versus 22.2 %). Among the patients who achieved an objective response, the median objective response was 9.7 months for the PAC arm and 9.4 months for the PAC/BEV arm.

Table 24. Objective Response^a

	PAC N = 243	PAC/BEV N = 229
No. of patients with objective response (%)	54 (22.2%)	112 (48.9%)
Complete response	0 (0.0%)	0 (0.0%)
Partial response	54 (22.2%)	112 (48.9%)
Difference in response rate (%)	26.7%	
95% CI ^b	(18.4%, 35.0%)	
p-value ^c	< 0.0001	
Median duration of response among responders	9.7 months	9.4 months

a: Only patients with measurable disease

b. by the standard normal approximation.

c: Cochran-Mantel-Haenzel test stratified by disease-free interval (≤ 24 , >24 months), number of metastatic sites (<3 , ≥ 3), adjuvant chemotherapy (yes, no), and ER status (positive, negative, or unknown).

Quality of Life

Quality of life was assessed by ECOG using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. The primary analysis for QOL was the change in the Trial Outcome Index (TOI) score from baseline to Week 17 for patients in arm A and B. In this primary analysis, patients with missing score following progressed or death were assigned 0, the worst score. If QOL scores were missing for any reason other than disease progression or death, they were not imputed and the patient was not included in the analysis. Only 572 patients were included in the analysis for change from baseline at Week 17 in TOI due to missing value.

The Sponsor reports that mean deterioration in QOL from baseline to Week 17 was statistically significant in favor of the PAC/BEV arm: -12.7 (SD 24.5) in PAC arm versus -6.6 (SD 18.5) in PAC BEV arm, p-value 0.0069 (Wilcoxon rank-sum test)

Reviewer's Comment: The clinical significance of this finding is unclear. Most notably, the quality of life assessment can not be used to support an Avastin label expansion because the study was open-labeled, and no information on concurrent medications was collected.

6.1.7 Other Endpoints

Not applicable.

6.1.8 Subpopulations

Reviewers comment: the following analyzes were performed by Hong Lu, PhD, Division of Biometrics. For additional subgroup analysis, please refer to Dr. Lu's statistical review.

Subgroup results of PFS and OS were analyzed for E2100 by gender, age and race. The results are shown in table 25 and 26 are generally consistent with that of the primary analysis.

Table 25. PFS Results by Race and Age

Baseline Risk Factor	Total n	# Events	PAC n	# Events	PAC/BEV n	# Events	Hazard Ratio	(95% CI)
All Patients	722	357	354	184	368	173	0.54	(0.44 - 0.67)
Age (yrs)								
< 40	59	37	32	20	27	17	0.54	(0.26 - 1.09)
40 - 64	496	243	239	121	257	122	0.51	(0.39 - 0.66)
≥65	167	77	83	43	84	34	0.67	(0.42 - 1.05)
Race								
White	550	268	266	136	284	132	0.54	(0.42 - 0.69)
Non-White	172	89	88	48	84	41	0.55	(0.36 - 0.86)

Table 26. OS Results by, Race and Age

Baseline Risk Factor	Total n	# Deaths	PAC n	#Deaths	PAC/BEV n	# Deaths	Hazard Ratio	(95% CI)
All Patients	722	481	354	238	368	243	0.93	(0.78 - 1.11)
Age (yrs)								
< 40	59	38	32	20	27	18	1.06	(0.56 - 2.00)
40 - 64	496	326	239	169	257	157	0.77	(0.62 - 0.96)
≥ 65	167	117	83	49	84	68	1.55	(1.07 - 2.25)
Race								
White	550	377	266	186	284	191	0.91	(0.75 - 1.12)
Non-White	172	104	88	52	84	52	1.01	(0.68 - 1.48)

Results of other subgroup analyses for PFS for study E2100 are shown in Table 27. The subgroup results for PFS are generally consistent with that of the primary analysis with hazard ratios below 1, except for the ER status "unknown group which had only 1 event in the PAC arm and 2 events in the PAC/BEV arm.

Table 27. PFS Results by Other Subgroups

Baseline Risk Factor	Total n	# Events	PAC n	# Events	PAC/BEV n	# Events	Hazard Ratio	(95% CI)
All Patients	722	357	354	184	368	173	0.54	(0.44 - 0.67)
Region								
North America	663	327	324	167	339	160	0.55	(0.44 - 0.68)
Rest of the World	59	30	30	17	29	13	0.43	(0.19 - 0.94)
Disease Status								
Locally recurrent	12	6	4	1	8	5	0.83	(0.09 - 8.04)
Metastatic	709	351	349	183	360	168	0.54	(0.44 - 0.67)
Disease-Free Interval (mo)								
≤24	296	163	146	81	150	82	0.58	(0.42 - 0.79)
< 24	426	194	208	103	218	91	0.50	(0.38 - 0.67)
ER Status								
Positive	446	211	223	103	223	108	0.59	(0.44 - 0.78)
Negative	265	143	127	80	138	63	0.44	(0.31 - 0.61)
Unknown	11	3	4	1	7	2	1.70	(0.15 - 19.07)
ER/PR/HER2 combined								
Negative	232	125	110	67	122	58	0.49	(0.34 - 0.70)
All others	490	232	244	117	246	115	0.57	(0.44 - 0.75)
HER2 status								
Positive	15	10	6	6	9	4	0.00	(0.00 -)
Negative	650	317	316	162	334	155	0.57	(0.45 - 0.71)
Unknown	57	30	32	16	25	14	0.42	(0.19 - 0.93)
Number of metastatic sites								
< 3	514	239	252	125	262	114	0.53	(0.41 - 0.69)
≥3	208	118	102	59	106	59	0.56	(0.38 - 0.81)
Measurable Disease at baseline								
Yes	472	248	243	125	229	123	0.66	(0.51 - 0.85)
No	250	109	111	59	139	50	0.37	(0.25 - 0.54)
SLD of target lesions – IRF								
≤Median	238	119	116	56	122	63	0.72	(0.50 - 1.03)
> Median	234	129	127	69	107	60	0.63	(0.44 - 0.91)
Prior adjuvant hormone therapy								
Yes	343	158	175	84	168	74	0.56	(0.41 - 0.77)
No	379	199	179	100	200	99	0.52	(0.39 - 0.70)
Metastatic/Recurrence hormone therapy								
Yes	262	121	128	61	134	60	0.53	(0.37 - 0.77)
No	460	236	226	123	234	113	0.55	(0.43 - 0.72)
Prior adjuvant chemotherapy								
Yes	475	232	231	121	244	111	0.47	(0.36 - 0.61)
No	247	125	123	63	124	62	0.70	(0.49 - 1.01)
Prior taxane therapy								

Yes	142	73	68	39	74	34	0.33	(0.20 - 0.54)
No	580	284	286	145	294	139	0.60	(0.47 - 0.76)
Prior anthracycline therapy								
Yes	364	183	180	97	184	86	0.53	(0.41 - 0.69)
No	358	174	174	87	184	87	0.56	(0.38 - 0.81)
Bone only								
Yes	63	18	27	10	36	8	0.28	(0.10 - 0.79)
No	658	339	326	174	332	165	0.58	(0.46 - 0.72)

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Not additional analysis of clinical information relevant to dosing recommendation was conducted for this application.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.11 Additional Efficacy Issues/Analyses

Non-Measurable Disease at Baseline Subgroup

E2100 included patients with measurable or non-measurable disease at baseline. A total of 197 patients (81 in PAC arm and 116 in PAC/BV arm) were reported by ECOG to have non-measurable disease at baseline. This number was significantly higher based on the IRF independent review. IRF identified 250 patients with non-measurable disease at baseline (111 in PAC, 139 in PAC/BEV). Among the 197 patients with non-measurable disease assessed by ECOG, 74 patients were assessed as having measurable disease by IRF due to differences in radiographic interpretations.

The reasons for ECOG measurable disease patient being assessed as non-measurable disease by IRF were missing baseline scans, patients had clinical exam lesion (per IRF charter, all lesions assessed by physical examination were to be incorporated into the IRF assessment as non-target, or non-measurable disease), differences in radiographic interpretation, image quality assessment or no obvious reason could be accounted for the difference.

To assess the impact of disease measurability on PFS, a sensitivity analysis was conducted in measurable and non-measurable disease subgroups per IRF. Results are shown in Table 28.

Table 28. Exploratory Analysis according to Disease Measurability per IRF

Measurable Disease at baseline	Total N	# Events (Censored)	PAC N	# Events (Censored)	PAC/BEV N	# Events (Censored)	HR	(95% CI)
Yes	472	248 (224)	243	125 (118)	229	123 (106)	0.66	(0.51 - 0.85)
No	250	109 (141)	111	59 (52)	139	50 (89)	0.37	(0.25 - 0.54)

Reviewer's comment: while assessing progression in the measurable disease can be readily done by RECIST criteria, assessing progression in the non-measurable disease is more difficult. Because RECIST response categories are assigned based on the change in the burden measurable disease, non measurable disease generally takes in to account complete response or in rare occasions, when clear progression in non-measurable disease occurs such that overall progression of disease would be considered to be occurred by the investigators. The determination of progression can not be objectively determined in patients with non-measurable disease. The large number of patients with non-measurable disease enrolled in E2100 is of concern, but exploratory analysis finding is consistent with that of the primary analysis.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Datasets from pivotal E2100 were used to evaluate safety of bevacizumab in combination with paclitaxel in patients with metastatic breast cancer. Case Report forms and patient narratives were reviewed. Results from AVF2119g provided additional supporting safety information.

7.1.2 Adequacy of Data

The data collection in E2100 was inadequate to provide a comprehensive assessment of adverse events associated with the use of bevacizumab plus paclitaxel. The following information was not collected in the E2100 study:

- Prior medical and surgical histories
- Vital signs and physical findings
- Patient height and weight
- ECOG performance status
- Clinical laboratory data
- Grade 1-2 adverse events

- Date of onset and resolution of adverse events
- Adverse events leading to treatment discontinuation
- Concomitant therapies and reason to initiate non-protocol treatment.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

Safety data from studies E2100 and AVF2119g (Section 5.3.2) were analyzed independently.

7.2 Adequacy of Safety Assessments

7.2.1. Overall Exposure at Appropriate Doses/Durations and Demographics of Target

Because E2100 study did not capture the height, weight, or BSA or the patients, assumptions were made by Genentech to estimate overall drug exposure. Drug exposure was estimated as the highest dose of drug given from first cycle divided by 10, and BSA estimated as the highest paclitaxel dose from the 1st cycle divided by 90.

As shown in Table 29, patients in the PAC/BV received more paclitaxel in total, but with overall lower dose intensity than paclitaxel alone.

Table 29. Estimated Drug Exposure[^]

	PAC N = 342	PAC/BV N = 358	
		PAC 358	BEV 358
Total duration of treatment Median (range)	5 months (0 – 25)	9 months (0-35)	
No. of cycles/patient Median (range)	6 (1-26)	10 (1-38)	
Total cumulative dose Median (range)	1440 mg/m ² (90-6744)	1926 mg/m ² (90-7510)	180 mg/kg (10-760)
Relative dose intensity (%) Median (min – max)	95.3% (33.3-131.9)	85.5% (12.1-105.6)	92.9% (38.5 – 145.0)

[^] Non-EPP patients only. Data from EPP patients are not available

Overall, patients in the PAC/BV arm required more frequent dose modifications/omissions, delays and reductions than paclitaxel alone arm, due to the higher incidence of adverse events (Table 30).

Table 30. Dose Modification and Delays

	PAC N=348 (%)	PAC/BV N=363(%)	
Dose modification/omission	226 (64.9)	321 (88.4)	
	N=342	N=358	
Dose delay [^] (≥ 1 week)	100 (29.2)	148 (41.3)	
Dose omission [^]	N=342	PAC N=358	BV N=358
	81 (23.7)	146 (40.8)	166 (46.4)
Mean	0.4	1.0	0.9
Range	0-7	0-12	0-14
Dose reduction [^]	N=342	N=358	N=358
>15% dose reduction	112 (32.8)	176 (49.2)	11 (3.1)

Compiled from Applicants Table 14.3/7, 14.3/9, 14.3/10

7.2.1 7.2.2 Explorations for Dose Response

No exploration for dose response was conducted.

7.2.2 7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or In Vitro Testing was conducted.

7.2.3 7.2.4 Routine Clinical Testing

Routine clinical testing results, i.e., clinical laboratory, vital signs, performance status, physical exam findings and ECGs were not collected in the E2100 study.

7.2.4 7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolic, clearance, and drug interaction workup was conducted during the E2100 study.

7.2.5 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable for this supplemental BLA.

7.3 Major Safety Results

7.3.1 Deaths

Table 31 shows all deaths reported for the study with the Applicant's attribution of cause of death. The majority of the patients died due to disease progression. Death was attributed to protocol treatment in one patient by the Applicant; however, review of the CRF revealed that the patient (ID # 21088, PAC arm) died of bowel obstruction caused by metastatic breast cancer. There were no deaths attributed to protocol treatment in the PAC/BV arm, by the Applicant.

Table 31. All Deaths *

Primary cause of death	PAC (348)	PAC/BV (363)
All deaths up to data cut-off	256 (73.6)	255 (70.2)
Due to this disease	241 (69.3)	243 (66.9%)
Due to protocol treatment	1 (0.3%)	0 (0%)
Due to other cause	7 (2)	9 (2.5%)
Unknown	7 (2)	3 (0.8)

*From ECOG CRF (Deaths reported as of June 6, 2007)

Deaths on study or within 30 days of end of study treatment occurred in 19 patients. There were 12 deaths in the PAC/BV arm and 7 deaths in the PAC arm in this category. The attribution of death by the Applicant and the FDA is shown in Table 32 and 33. Upon review of the case narratives and case report forms, the FDA disagrees with the Applicant's cause of death attribution in several instances. Most importantly, in the PAC/BV arm, five out of the twelve deaths were found to be possibly/definitively related to the protocol treatment (refer to Table 33 for summary of case narratives).

Table 32. Deaths on Study or within 30 days of End of Study Treatment Applicant * and FDA's Attribution of the cause of death

Cause of death	PAC		PAC/BV	
	Applicant	Reviewer	Applicant	Reviewer
Death on study/within 30 days	7	7	12	12
Due to protocol treatment				
Definite	0	0	0	2
Probable				3
Due to this disease	4	3	8	4
Due to other cause	2	1	4	1
Unknown	1	2	0	2
Insufficient information	0	1	0	0

* From Applicant Table 14.3/27

Applicant listing 2, response to 10/8/07 FDA query

FDA review of case narratives and case report forms revealed six deaths possibly/definitively attributed to protocol therapy. Five deaths occurred during study or within 30 days of last protocol therapy and one patient died 7 weeks after discontinued from protocol due to toxicity. Summary of case narratives and the applicant's attribution of the cause of death are shown in Table 33.

A review of case report forms of patients who died within 30 days of treatment in the paclitaxel alone arm did not revealed any deaths attributed to protocol therapy (Table 32). As indicated above, death was attributed to protocol treatment in one patient by the Applicant; however, review of the CRF revealed that the patient (ID # 21088, PAC arm) died of bowel obstruction caused by metastatic breast cancer 36 months after the last dose of paclitaxel.

Table 33. Summary of Deaths Narratives and Cause of Death Attributions by The Applicant and FDA (within 30 days of end of study)

Patient ID	Narrative and/or CRF summary	Applicant	NCI/Inv	FDA
PAC arm				
21284	56yof, 2 cycles PAC. Sudden death at home. Cause unknown	Other cause	Other cause	Unknown
26024	80yobf with history of hyperthyroidism stopped taking medications, developed supraventricular arrhythmia, cardiac LV dysfunction, aspiration pneumonia and dead. Dead attributed to hyperthyroidism	Other cause	Other case	Agree
21042	54 yo received 3 cycle of PAC, progressive, respiratory failure due to pericardial, pleural effusion (tumor)	Breast ca	Breast ca	Agree
21129	63yo received 3 cycles of PAC, admitted for confusion, gr4 hyperglycemia, dehydration, anemia. Died 8 days later.	Breast ca	-	Insufficient information, other cause?
21412	50 yo, 9 cycles of PAC, syncopal episode with trauma to C2, MRI dx brain metastasis and leptomenigeal carcinomatosis. Expired due to disease progression	Breast ca	Breast ca	agree
23006	57yo dx with brain metastasis, did while hospitalized.	Breast ca	Breast ca	agree

26030	74yof, received 6 cycles PAC, sudden dead at home	Unknown	Unknown	Unknown
BEV/PAC				
21314	84 years-old patient, received 3 cycles of PAC/BEV, developed acute abdomen with gastrointestinal perforation, sepsis, respiratory failure and death.	other cause	Possible	Possible/Definite
21403	73 years-old patient, 22 days after bevacizumab treatment developed progressive fatigue, pneumonitis, and fatal cardiac ischemia and/or infarction and LV dysfunction.	other cause	Possible	Possible
22025	52yo, sudden death at home after 3 cycles of BEV/PAC	Other cause	Possible	Unknown
26004	66 years-old patient was admitted with severe diarrhea with black tarry stool and abdominal pain after 11 cycles of PAC/BEV. Symptoms were attributed to diverticulitis and PAC/BEV. 22 days after symptoms were reported; the patient became hypotensive, bradycardic and died.	other cause	Possible, unknown	Possible/Definite
21010	79 years old patient, receive 6 cycles PAC/BEV, developed severe diarrhea, fatigue, muscle weakness and lethargy and death 11 days after last dose of protocol.	Breast ca	Unknown	Possible
21156	71yo, sudden dead at home 13 days after 1 st cycle of BEV/PAC. Exact etiology of death and relationship to study treatment are unknown	Breast ca	Unknown	Unknown
21258	64 years old patient, 6 cycles PAC/BEV, developed abdominal pain with gastrointestinal perforation, neutropenia, sepsis and death.	Breast ca	Possible	Possible/Definite

21262	48yo, abdominal pain, hematuria, ascites, neutropenia, infection, portal vein thrombosis. CT extensive liver metastasis, ascites, effusion. Died after 7 cycles of BEV/PAC of multi organ systemic failure due to metastatic breast cancer	Breast a	Breast cancer	Breast cancer
21407	46yof, 2 cycles BEV/PAC, elevate bilirubin, GI bleed, bone pain, fatigue, anemia. CT scan show marked expansion of tumor burden (celiac axis node, iliac psoas, gluteal muscle, pancreatic head)	Breast ca	Breast cancer	Breast ca
21432	57yo, 3 cycles of BEV/PAC, fever, neutropenia, intractable bone pain. MRI extensive bone involvement.	Breast ca	Breast cancer,	Agree
22019	72yo, 2 cycles PAC/BEV, severe bone pain, possible spinal cord compression, lumbar spine fractures, and new liver metastasis. Died as a results of metastatic breast ca	Breast ca	Breast ca	Agree
27009	44yo, 6 cycles BEV/PAC, off therapy due to progressive disease. Received post-protocol chemotherapy, with neutropenia, fever, hospitalization	Breast ca	Breast ca	Cause of death unknown. Unlikely to be related to protocol therapy.
Death > 30 days of end of study				
21390	69 years old patient, discontinued protocol therapy after 3 cycles of BEV/PAC due to grade 4 proteinuria. Patient had a fatal acute myocardial infarction 7 weeks after being discontinued from protocol due to nephrotic syndrome	Death due to other cause		Possible/Definite

Conclusion: Fatal adverse reactions attributed to bevacizumab plus paclitaxel occurred in 6/363 (1.7%). Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal pain/weakness/hypotension (2).

7.3.2 Nonfatal Serious Adverse Events

Refer to section 7.3.4 and 7.3.5 below.

7.3.3 Dropouts and/or Discontinuations

A total of 142 patients (19.6%) discontinued therapy due to toxicity/side effects/complications, 70 in PAC arm (20%), 72 (19.8%) in PAC/BV arm. The specific adverse event(s) leading to treatment discontinuation was not collected in the E1200 study.

Per FDA's request during the review process, Genentech provided the following information based on occurrence of adverse events and temporal association with the discontinuation of therapy. The most common causes of treatment discontinuation in the PAC arm were neuropathy (60%) and allergic reactions (5.7%). Common causes of treatment discontinuation in the PAC/BV arm based on temporal association were: neuropathy (25%), thrombosis (12.5%), proteinuria (9.7%), hypertension (6.0%), arterial thromboembolic event (5.6%), left ventricular dysfunction (5.6%), fatigue (5.6%) and multiple medical events.

7.3.4 Significant Adverse Events

NCI-CTC Grade 3 -5 Adverse Events

Table 29 shows treatment emergent Grade 3-5 adverse events with ≥ 1 % difference in incidence between the two treatment arms. The addition of bevacizumab to paclitaxel led to a 20.2 % increase in grade 3-5 adverse events when compared to paclitaxel alone. This incidence of serious adverse events in the treatment arm is higher (71.1%) with NCI AdEERS reporting; however, because SAEs associated with the control arm were not reported to AdEERS, a direct comparison can not be made.

Death associated to treatment was higher in the PAC/BV arm when compared to PAC alone arm (3.0 % versus 2.0 %). The incidence of death was higher (4.1%) with the AdEERS reporting (refer to section regarding Death on Study below).

The increased incidence of grade 3-5 adverse events in the PAC/BV arm was observed with all major organ systems: neurologic, cardiovascular, constitutional, gastrointestinal, infectious, renal, metabolic and pulmonary, hepatic, skin, musculoskeletal, and bleeding are highlighted in Table 34. In contrast, only venous thromboembolic events occurred in higher incidence in the paclitaxel alone arm (4.3 % versus 2.5%).

Table 34. Treatment Emergent Grade 3-5 Adverse Events with ≥ 1 % Difference in Incidence

AE	PAC N = 348 (%)	PAC/BV N=363 (%)	AdEERS and/or CRF
Total	176 (50.6)	257 (70.8)	258 (71.1)
Grade 5	7 (2.0)	11 (3.0)	15 (4.1)
Grade 4	32 (9.2)	44 (12.0)	49 (13.5)
Grade 3	137 (39.4)	202 (55.6)	194 (53.4)
Neurology	74 (21.3)	109 (30.0)	110 (30.3)
Sensory	61 (17.5)	88 (24.2)	88 (24.2)
Motor	6 (1.7)	11 (3.0)	11 (3.0)
Syncope	2 (0.6)	8 (2.2)	9 (2.5)
Cerebrovascular ischemia	0	7 (1.9)	9 (2.5)
Cardiovascular	28 (8.0)	79 (21.8)	83 (22.9)
HTN	5 (1.4)	57 (15.7)	58 (16.0)
Thrombosis/embolism	15 (4.3)	9 (2.5)	11 (3.0)
Left Ventricular dysfunction	1 (0.3)	5 (1.4)	8 (2.2)
Cardiac ischemia	0	3 (0.8)	4 (1.1)
Pain	33 (9.5)	59 (16.3)	62 (17.1)
Gastrointestinal	21 (6)	57 (15.7)	58 (16.0)
Vomiting	8 (2.3)	20 (5.5)	20 (5.5)
Diarrhea	5 (1.4)	17 (4.7)	17 (4.7)
Dehydration	3 (0.9)	12 (3.3)	12 (3.3)
Constitutional/Fatigue	18 (5.2)	39 (10.7)	39 (10.7)
Infection/fever/neutropenia (Gr 3-5)	20 (5.7)	50 (13.8)	52 (14.3)
Metabolic/laboratory	15 (4.3)	22 (6.1)	23 (6.3)
Pulmonary/dyspnea	18 (5.2)	23 (6.3)	24 (6.6)
Renal/genitourinary	2 (0.6)	16 (4.4)	17 (4.7)
Proteinuria	0	10 (2.8)	11 (3.0)
Hepatic	9 (2.6)	14 (3.9)	16 (4.4)
SGOT	5 (1.4)	9 (2.5)	9 (2.5)
Dermatology/skin	6 (1.7)	15 (4.1)	19 (5.2)
Musculoskeletal/muscle weakness	9 (2.6)	16 (4.4)	16 (4.4)
Hemorrhage	1 (0.3)	6 (1.7)	8 (2.2)

The most common grade 3-4 adverse event observed in either arm was sensory neuropathy (24.2% in the PAC/BV arm versus 17% in the PAC arm). Per Genentech, after adjusting for exposure to paclitaxel and duration of adverse event reporting, the incidences of neuropathy were found to be comparable between the treatment arms. The Applicant concluded, and the FDA agrees, that the increased incidence of neuropathy observed in the PAC/BV arm is most likely secondary to increased cumulative paclitaxel exposure (refer to Table 29, Estimated Drug Exposure) and not intrinsic to bevacizumab therapy.

7.3.5 Submission Specific Primary Safety Concerns

Significant Serious Adverse Events Known to be Associated with Bevacizumab

The incidence of significant adverse events known to be associated with bevacizumab and the severity are presented in Table 35 and compared with paclitaxel monotherapy arm.

Hypertension, neutropenia with infection were the most common events (15.7 and 17.1 %), followed by proteinuria and arterial thromboembolic events and hemorrhage. The overall number and severity of events were slightly higher with AdEERS reporting system.

Since the date of onset and resolution of the events were not collected in this study, the time to recovery of these events is not known.

Death associated with study drug is further discussed in section 7.3.1

Table 35. Serious AE Known to Be Associated with Bevacizumab

	PAC (348)	PAC/BV (363)	AdEERS/CRF
Hypertension			
Total	5 (1.4)	57 (15.7)	58 (16.0)
Grade 3	5 (1.4)	56 (15.4)	56 (15.4)
Grade 4	0	1 (0.3)	2 (0.6)
Proteinuria			
Total		10 (2.8)	11 (3.0)
Grade 3	0	7 (1.9)	7 (1.9)
Grade 4		3 (0.8)	4 (1.1)
Arterial Thromboembolic Events			
Total	0	10 (2.8)	13 (3.6%)
Cerebrovascular ischemia			
Total		7 (1.9)	9 (2.5)
Grade 3		4 (0.8)	3 (0.8)
Grade 4	0	3 (1.1)	6 (1.7)
Cardiac ischemia			
Total		3 (0.8)	4 (1.1)
Grade 3	0	1 (0.3)	1 (0.3)
Grade 4		0	1 (0.3)
Grade 5		2 (0.6)	2 (0.6)
Venous Thromboembolic Events			
Total	15 (4.3)	9 (2.5)	11 (3)
Grade 3	8 (2.3)	8 (2.2)	10 (2.8)
Grade 4	7 (2.0)	1 (0.3)	1 (0.3)
Bleeding/Hemorrhage			
Total	1	6 (1.7)	8 (2.2)
Grade 3	1 (0.3)	5 (1.4)	6 (1.7)
Grade 4	0	1 (0.3)	2 (0.6)
Congestive Heart Failure			

Total	1 (0.3)	5 (1.4%)	8 (2.2)
Grade 3	0	5 (1.4)	7 (1.9)
Grade 4	0	0	1 (0.3)
Grade 5	1 (0.3)	0	0
Gastrointestinal Perforation			
Total		2 (0.6)	2 (0.6)
Grade 4	0	2 (0.6)	0
Grade 5		0	2 (0.6)
Gastrointestinal Fistula			
Grade 4	0	1 (0.3)	1 (0.3)
Neutropenia/infection			
Total	28 (8)	62 (17.1)	63 (17.4)
Grade 3	16 (4.6)	39 (10.7)	40 (11.0)
Grade 4	12 (3.4)	22 (6.1)	22 (6.1)
Grade 5	0	1 (0.3)	1 (0.3)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Grade 1-2 adverse events were not collected in the E2100 study; hence a common adverse events profile for bevacizumab in combination with paclitaxel can not be established.

7.4.2 Laboratory Findings

Laboratory data was not collected in the E2100 study.

7.4.3 Vital Signs

Vital signs were not collected in the E2100 study.

7.4.4 Electrocardiograms (ECGs)

ECGs were not collected in the E2100 study.

7.4.5 Special Safety Studies

No special safety studies were conducted during study E2100.

7.4.6 Immunogenicity

Immunogenicity studies were not performed in the E2100 study.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The dosage of bevacizumab evaluated in E2100 study was 10 mg/kg administered intravenously over 90 minutes.

7.5.2 Time Dependency for Adverse Events

E2100 did not collect time of onset and resolution of adverse events.

7.5.3 Drug-Demographic Interactions

No specific drug-demographic interaction studies were conducted.

7.5.4 Drug-Disease Interactions

No specific drug-disease interaction studies were conducted in E2100 study.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted in E2100 study.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not conducted during study E2100.

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction studies were conducted or data collected during the E2100 study.

7.6.3 Pediatrics and Effect on Growth

No additional study or data collection on growth effect were conducted during the E2100 study.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose incidence was reported in the E2100 and E2119g studies. There is no known abuse potential or withdrawal phenomena associated with bevacizumab.

7.7 Additional Submissions

Safety data of bevacizumab in combination with capecitabine (study AVF2119g) and monotherapy (AVF0776g) for 2nd and 3rd line treatment of patients with metastatic breast cancer are summarized in section 5.3.2 and 5.3.3

8 Post marketing Experience

Several safety issues identified from the Avastin post marketing experience have been included in the Avastin label since its initial approval:

- Arterial thromboembolic events and infusion reactions (December 2004),
- Gastrointestinal perforation (April 2006),
- Reversible posterior leukoencephalopathy syndrome (RPLS) and nasal septum perforation (September, 2006) and
- Non-gastrointestinal fistula formation (October, 2007).

9 Appendices

9.1 Literature Review/References

The reviewer conducted selected searches of the literature for selected issues pertinent to this supplement. References submitted by the Applicant were reviewed.

- FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: <http://www.fda.gov/cder/guidance/7478f1.htm>
- Response Evaluation: beyond RECIST, E.A. Eisenhauer, NCIC Clinical Trials Group, Queens University, Kingston, CN, Canada, Annals of Oncology 18 (Supplement 9): 29 - 32, 2007
- When You Look Matters: The Effect of Assessment Schedule on Progression-Free Survival. Panageas, KS, Ben-Porat, L, Dickler MN, Chapman, PB, Schrag D. JNCI 2007 99 (6): 428-432

9.2 Labeling Recommendations

FDA made the following recommendations for change in the CLINICAL STUDIES, INDICATIONS AND USAGE and ADVERSE EVENTS sections of the package insert. Genentech agreed with the recommendations.

4 Page(s) Withheld

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

 √ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Other agreed additions to the label:

ADVERSE REACTIONS

The most serious adverse reactions in patients receiving Avastin were:

- Congestive Heart Failure (see **WARNINGS**)

DOSAGE AND ADMINISTRATION

Metastatic Breast Cancer

The recommended dose of Avastin is 10 mg/kg, as an IV infusion every 14 days.

9.3 Advisory Committee Meeting

The supplemental BLA was presented to the Oncology Drug Advisory Committee (ODAC) on December 5, 2007. In response to the question “Are the data provided sufficient to establish a favorable risk/benefit analysis for the use of bevacizumab plus paclitaxel for first-line treatment of patients with metastatic breast cancer?” the vote was 5 “no” and 4 “yes”.



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

CLINICAL REVIEW AND EVALUATION

BLA/Serial No 125085/91

Drug Name Avastin®/bevacizumab

Indication 1st Line Treatment of Recurrent or Metastatic Breast Carcinoma

Applicant Genentech, Inc

Submission Date May 23, 2006
PDUFA Date November 23, 2006
Review Completion September 8, 2006

Medical Division Division of Biological Oncology Products, OODP
Clinical Reviewer Lee Pai-Scherf, M.D. LHP-5 9/8/06
Team Leader Kaushikkumar Shastri, MD PK for KS 9-8-06
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Biometrics Division Biologics and Therapeutics Statistical Staff
Statistical Reviewer Hong Lu, PhD
Team Leader Mark Rothman, PhD



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

Memorandum

Date: September 8, 2006
From: Lee Pai-Scherf, MD, Medical Officer *LHP-S 9/8/06*
Division of Biologic Oncology Products, OODP, CDER
Through: Kaushikkumar Shastri, MD, Team Leader *Prepared for K Shastri 9-8-06*
Division of Biologic Oncology Products, OODP, CDER
To: File
Subject: Clinical Review of supplemental Biological License Application
STN 125085\91

This review is in response to the supplemental Biologics License Application (sBLA) submitted by Genentech Inc. to support the use of Avastin® in combination with taxane-based chemotherapy for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer. This sBLA was submitted on May 23, 2006, the PDUFA due date is November 23, 2006.

Review of the information and data by the Division of Biologic Oncology Products determined that the information and data submitted to support the sBLA are inadequate for final approval action at this time. The review team recommends that a complete review letter, outlining the deficiencies of the sBLA be issued to Genentech Inc.

I. Background

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

2. Brief Overview of Clinical Program

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. In June 2006, approval was granted for bevacizumab to be used in combination with FOLFOX4 chemotherapy as second line treatment in patients with recurrent, advanced, or metastatic colorectal cancer.

In this supplemental Biological License application, approval is sought for Avastin in combination with taxane based chemotherapy for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer.

b(4)

Data from the following studies were submitted to support this sBLA:

- Primary study (efficacy and safety)
 - E2100, a randomized, open-label, phase III trial of paclitaxel vs. paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. The study was supported by the National Cancer Institute (NCI), conducted by the Eastern Cooperative Oncology Group (ECOG)
- Supportive studies (safety)
 - AVF2119g, a randomized, open-label, phase III trial of capecitabine vs. capecitabine plus bevacizumab in patients with previously treated metastatic breast cancer. The study enrolled a total of 462 patients.
 - AVF0776g, a single arm, phase I/II trial of bevacizumab in patients with relapsed metastatic breast cancer. The study enrolled 75 patients.

3. Pre-Submission Regulatory Activity

Study E2100 was first submitted on October 19, 2001, under NCI's IND 7921. On May and October 2002, the FDA provided comments and recommended revisions to the protocol to address the deficiencies in the statistical analysis plan. The study was not originally designed as a registration trial.

On October 28, 2004, a teleconference was held at the request of Genentech Inc. to discuss the adequacy of the study E2100 to support a new indication for the treatment of patients with locally recurrent or metastatic breast cancer. Following are excerpts of the meeting:

- *The FDA noted that E2100 may not be adequate to support licensure due to the non-blinded nature of the study and the lack of pre-specified, detailed and objective radiological and clinical parameters for determination of disease progression.*
- *Given the deficiencies in the study design (e.g., unblinded study and no blinded Independent Review Committee), FDA stated that a determination of*

- the adequacy of the study to support a new indication would require analysis of the study results and assessment of the conduct of the study*
- *In support of regulatory approval for the proposed new indication, Genentech would have to provide information regarding the effect of bevacizumab on survival data*
 - *FDA noted that in reviewing the results of the E2100 study, data from AVF2119g, a phase 3 study of bevacizumab plus capecitabine in patients with refractory breast cancer, which failed to demonstrate efficacy, would also be considered*
 - *FDA further noted that the results of this single study may not be sufficiently robust and thus may need to be supported by a second positive adequate and well-controlled study in this population.*
 - *Time-to-treatment failure (TTF),) the proposed primary endpoint by NCI was not an acceptable endpoint for labeling. Genentech asked if PFS is an adequate endpoint for full approval. FDA replied that it depends on the overall dataset and magnitude of PFS. Genentech would provide survival data at the time of the PFS analysis*

Following the October 2004 teleconference, Genentech submitted a revised Statistical Analysis Plan on April 5, 2005, revising the primary endpoint to PFS.

At the first planned ECOG interim efficacy analysis on April 6, 2005, the ECOG Data Monitoring Committee concluded that the study had met its primary endpoint, improvement in PFS in patients who received bevacizumab plus paclitaxel compared with paclitaxel alone. Results were presented at the May 2005 American Society of Clinical Oncology (ASCO) meeting.

A pre-sBLA meeting was held on September 28, 2005 to discuss plans for Genentech to submit a sBLA based on the results of E2100 study. During the meeting, the FDA agreed that E2100 can form the basis of the primary efficacy evaluation of the sBLA. FDA noted that the endpoint of PFS would support an accelerated approval. Genentech was asked to submit data on overall survival at the time of filing. Mature data concerning overall survival would be requested as a post-marketing commitment and would convert the sBLA from accelerated approval to regular approval.

II. Summary of Clinical Findings

E2100 is a randomized, open-label, phase III trial of paclitaxel vs. paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Patients with histologically or cytologically confirmed adenocarcinoma of the breast with measurable or non-measurable locally recurrent or metastatic disease were enrolled. Eligible patients were randomized in a 1:1 ratio to receive paclitaxel (90 mg/m² iv every week for 3 weeks followed by 1 week of rest) plus bevacizumab (10mg/kg following paclitaxel on weeks 1 and 3) or paclitaxel alone. Treatment was administered until disease progression or unacceptable toxicity. The randomization was stratified by

disease-free interval (< 24, ≥ 24 months), number of metastatic sites (< 3, ≥ 3), prior receipt of adjuvant chemotherapy (yes, no), and ER status (positive, negative, and unknown). The primary efficacy analysis compared the PFS between the paclitaxel plus bevacizumab arm and the paclitaxel alone. Secondary efficacy endpoints included overall survival, objective response rate, duration of objective response, and QOL.

Between December 21, 2001 and May 26, 2004, 722 patients were randomized (354 patients to the paclitaxel alone arm and 368 to the paclitaxel plus bevacizumab arm). Review of the E2100 Clinical Study Report and supporting SAS datasets by the review team identified the following deficiencies, some of which have been previously communicated to Genentech during the review process:

1. The E2100 Clinical Study Report states that ECOG continues to collect enter and clean all study data, including patient information, safety and efficacy data, following the 30 December 2005 data transfer to Genentech. Data submitted to support a license application must be locked, data collection completed, cleaned up, and finalized. Genentech must submit a complete clinical dataset as of a specified cut-off date; the selected cut-off date should be justified based on timing of interim analysis resulting in public dissemination of study results. All data tables and line listings, including updated safety information should be updated for accuracy and completeness.
2. As indicated in our letter to Genentech on July 6, 2006, the key efficacy endpoints of PFS and objective response rate analyses to support this sBLA were based on Genentech's review of ECOG's central review of investigator-reported tumor data from E2100 study. Tumor data used by ECOG and Genentech consists solely of the investigator-reported tumor lesion measurements and comment fields. Given the subjective nature of the PFS endpoint, auditing to assess data integrity in a subset of the patients must be conducted. The review team provided Genentech with a list of 144 randomly selected patients for audit during the review process. An independent review committee charter was submitted on August 15, 2006 by Genentech and FDA comments were forwarded to the applicant on August 30, 2006. Depending on the results of this evaluation, a more extensive audit may be required.
3. E2100 Clinical Study Report states that patients enrolled at non-ECOG sites (35%) had only limited data entered into the ECOG clinical database. It further states that because collection of these data was incomplete, these data were not used in the analysis. The review team has serious concerns regarding the reliability and completeness of the clinical database. In order to verify the integrity of the data submitted to support licensure, Genentech must submit eligibility checklist and a complete set of case report forms for all 722 patients enrolled in the E2100 study for review.
4. As indicated in our letter of July 6, 2006, the data to determine patient eligibility and adequacy of the conduct of E2100 trial is incomplete. Eligibility assessed

using ECOG eligibility from is available in 605/722 patients (84%). ECOG case evaluation to determine protocol violation/deviation is available in only 261/722 patients (36%). This information is insufficient to determine if the trial supporting licensure was well conducted. Genentech must provide the eligibility and a complete dataset of case evaluation data for all 722 patients enrolled in the study. In addition, the applicant should provide the number of patients who were granted eligibility exceptions by treatment arm for all randomized patients as specified in the Statistical analysis plan of April 5, 2005.

5. Results of objective response presented in the CSR are based on a cutoff date of April 14, 2005. Based on Listing 16 2/4, a total of 188 patients (87 in the PAC arm and 101 in the PAC/BV arm) have unevaluable or unknown best confirmed response because the data is still being cleaned up. Genentech must submit a final and cleaned up result of objective response to support the application. Information for all randomized patients, with measurable and non-measurable disease must be provided.
6. Table 7, page 75 of the E2100 clinical study report indicates that 208/722 patients had no measurable disease at baseline (24.3% in the PC arm and 33.2% in the PC + bevacizumab arm). Genentech should clarify how the information of non-measurable disease was collected and provide further information on the site and extent of tumor involvement. Additionally, PATE.xpt, indicates that the variable "dismeas" is derived from baseline SLD. Genentech should provide information (program) on how "dismeas" was obtained.
7. Genentech should confirm that the following information required in the protocol monitoring schema was not collected during the conduct of the study:
 - a) Medical and surgical histories.
 - b) VS and physical findings
 - c) Height and weight
 - d) ECOG performance status
 - e) Clinical laboratory data
 - f) Onset date of an AE was not collected (reporting period – i.e., 3-cycle durations, if event was observed more than once during a reporting period, the highest grade was reported)
 - g) Adverse events that led to treatment discontinuation Grade 1 -2 AEs
 - h) Concomitant therapies were not collected in this study with the exception of Non-Protocol Therapy received prior to tumor progression. Excluded therapies were not specified in the protocol, and NPT was not defined in the protocol.
 - i) Reason to initiate Non-protocol treatment
 - j) Information on therapy initiated following disease progression, including chemotherapy in either arm or any possible bevacizumab in the paclitaxel alone arm patients.

8. Genentech made changes to the planned statistical analysis that is not acceptable. Summary results for all pre-specified analyses of the data, as described in the statistical analysis plan, must be included in the clinical study report.
 - a. Secondary endpoints include objective response rate and duration of objective response. As specified in the SAP, primary analysis for objective response rate will be performed using the ITT population and baseline measurable disease (yes, no) will be included as a stratification factor). Genentech must submit result of objective response rate and duration of objective response rate for all randomized patients, as specified in the SAP, section 3.4.2.b and 3.4.2.c pages 853-854. Genentech must provide dataset to support the findings. Datasets should provide sufficient information to determine the cause of progression in patients with non-measurable disease and to confirm progression in patients with clinical rather than measurable progression.
 - b. Secondary endpoint also includes Quality of Life assessment, as specified in the SAP of April 5, 2005. Genentech must provide results of QOL analysis as specified in the SAP, section 3.4.2.d, page 855.
 - c. Genentech should submit the following exploratory analysis as specified in the Statistical Analysis Plan, Section 3.4.3, pages 857-860):
 - OS and ORR analyses by baseline characteristics. The following demographic as baseline characteristics must be considered as specified in the SAP: disease-free interval (≤ 24 months, > 24 months), number of metastatic sites (< 3 , ≥ 3), adjuvant chemotherapy (yes, no), ER status (ER positive, ER negative, ER unknown), ECOG performance status at study entry ($0, \geq 1$), age ($< 40, 40-65, > 65$ years), sex, race (white, non-white), baseline sum of the longest diameters of all target lesions, and HER2 expression status by immunohistochemistry.
9. Datasets provided do not contain sufficient information to determine how patients with unevaluable and unknown response status were evaluated regarding PFS. Genentech must clarify how such patients were handled in the analysis of PFS.
10. Genentech should provide a summary of the number of missing response assessments per timepoint as specified in the Statistical Analysis Plan of April 5, 2006.
11. Genentech should provide a comprehensive efficacy results based on the interim analysis, including patient disposition, results for secondary endpoints, i.e., Table 2, 10-14, 17 and figures 3-4 in the CSR. For each reported subgroup analysis Genentech must include event numbers as well as Hazard Ratio.
12. Genentech should provide a dataset with the cut-off date of February 2005 (interim analysis) including all the variables in the current PATE.xpt data.

13. Genentech should provide SAS programs used for the derivation of Genentech's PFS and response outcome, i.e., variables pdfdt7, pfscen7, pdfdt8b, pfstime7, pfstime8b, pfcen8b, pdiadt7, pdia7, crspi7, crprdt7, trtpdif7, pftype8b, and pfstype7 in TUMORPAT.xpt.
14. There is insufficient and incomplete information to access the toxicity profile of Avastin in combination with paclitaxel. As stated above, the safety data of E2100 is incomplete, as ECOG and Genentech continued to collect, enter and clean up pre-existing data at the time of the sBLA submission. Genentech must submit a complete, cleaned up data set for review. All tables and line listings must be updated. Concerning the submitted information, we have the following comments and requests to the Sponsor:
 - a. There is insufficient information to evaluate the extent of drug exposure in E2100 study. In addition to number of cycles and number of doses received, please provide the cumulative dose (mg/m² or mg/kg), dose intensity (mg/m²/cycle or mg/kg/cycle), number of dose modifications, and number and length of dose delays/omission for each arm and for each agent, i.e., for bevacizumab plus paclitaxel arm, information should be provided for each agent separately. Genentech should provide data in individual line listing and in tabular format and a SAS data set.
 - b. Regarding dose modification/omission: 219 patients (63.7%) in the paclitaxel arm and 313 (87.4%) in the paclitaxel/bevacizumab arm had dose modification or omission. Genentech should provide the line listing and in tabular format, the reason, either planned or unplanned, that lead to dose modification /omission of paclitaxel, bevacizumab or paclitaxel and bevacizumab.
 - c. For the Paclitaxel/Bevacizumab arm, Genentech should identify the patients who discontinued bevacizumab and continued on paclitaxel alone and patients who discontinued paclitaxel and continued bevacizumab alone prior to disease progression.
 - d. Listing 16.2/13 provides deaths and study discontinuation due to toxicity of patients treated in the paclitaxel alone arm. Genentech should provide a similar listing for the paclitaxel and bevacizumab arm.
 - e. Listing 16.2/12 provides adverse events that occurred in temporal proximity to protocol therapy discontinuation. Genentech should provide in a tabular format, for the paclitaxel and paclitaxel plus bevacizumab arm the causes of AEs leading to (reported in temporal proximity) to treatment discontinuation.

- f. Adverse events reported to NCI AdEERS for the paclitaxel arm were submitted CTEP, but not provided to Genentech. These reports were sent to MedWatch. Genentech should provide copies of the MedWatch reports related to E2100 study.
- g. Genentech should provide a single adverse event dataset that includes all sources of adverse event collection including the E2100 toxicity form, AdEERS, Off Study Forms and MedWatch Reports. The dataset should be designed so that the collection source is identified and searchable.
- h. The case narratives provided in the sBLA are frequently incomplete and with discrepancies that do not allow a full understanding of the clinical picture. Following are two examples of incomplete and inconsistent patient narratives:

- Patient No. 26004: narrative describes a 66 years-old female patient, who died from a cause other than PD more than 30 days after the last dose of protocol therapy that was possibly related to bevacizumab. Narrative states that "the patient was randomized on 11 July, 2003... sites of disease involvement include bone... The date of the first protocol therapy administration was 17 July 2003. Between 8 January 2004 and 31 March 2004 (cycles 7-9), she experienced grade 3 sensory neuropathy. Data capture in the AdEERS database indicated that the patient experienced grade 3 abdominal pain, diarrhea with black tarry stools on 4 May, 2004. The patient's last dose of bevacizumab prior to the events was administered on 28 April 2004 (cycle 9)... The patient received treatment with paclitaxel only on 27 May 2004. On 27 May, 2204 she became hypotensive and bradycardic... pronounced death on _____ The next paragraph of the narrative states: "...The last date of protocol therapy administration was reported as 18 March 2004. The last cycle of bevacizumab (Cycle 9) was reported as 4 March 2004..."

b(4)

- Patient No. 21407: narrative describes a 44 year-old patients, with an event reported through AdEERS. The patient was randomized on 19 March 2004. Sites of disease involvement included the right gluteous. The date of first protocol therapy was 22 March 2004. The patient was seen in office for cycle 2 with fatigue and low blood counts. She received paclitaxel and bevacizumab and was admitted for pain control, anemia and lower extremity edema. She was discharged on _____ and died on _____ The date of disease progression was 29 April 2004. Narrative further states that patient had "Grade 5 constitutional symptoms (disease progression), Grade 4 increased bilirubin, Grade 4 bone pain, a Grade 3 GI bleeding event, Grade 3 increased prothrombin time, a grade 3 hypoxia were reported. This narrative is incomplete as it does not

b(4)

provide sufficient information regarding the patients' clinical picture. It is unclear the cause of the grade 4 bilirubin, the cause, the time of onset and resolution of GI bleeding or the clinical or radiological evidence to support disease progression.

Genentech must review and revise all case narratives accordingly. Narratives must be complete and contain the pertinent information necessary to make clinical sense. All reporting discrepancies between the CRF and AdEERS must be queried and solved by Genentech.

- i. To facilitate and expedite review, Genentech should provide in a tabular format, a list of all patients with narratives, with hyperlinks, page no. and the reason for the narrative reporting.

Patient ID	Hyperlink	Reason for Narrative Reporting	Page No.

15. Regarding financial disclosure:

- a. Genentech must provide signed financial disclosure statements for the following ECOG study administrative body:

Study Chairperson: Kathy D. Miller, MD
 Study co-chairperson: Robin Zon, MD
 Pathology co-chairperson Ann Thor, MD
 Statistician Molin Wang, Ph.D.
 QOL sub-committee chairperson David Cella
 Breast committee chairperson George W. Sledge Jr., MD
 Correlative co-chairperson Kathy D. Miller, MD
 Community co-chairperson Thomas Shaphner, MD
 NCCTG co-chairperson Edith Perez, MD
 NCIC CTG co-chairperson Tamar Shenkier, MD
 NSABP co-chairperson Melody Cobleigh, MD

It was noted that Dr. Kathy Miller (Study Chairperson) failed to reply to the Financial Disclosure Information requests (requests sent on 11/11/05 and 12/15/05).

- b. Genentech should provide the name/affiliation of the members of the ECOG Data Monitoring Committee (DMC) involved in E2100 data analysis. A signed financial disclosure statements for the DMC members must be provided.

16. CSR E2100, Section 6, page 20 states Data management was conducted in accordance with ECOG Policy and Standard Procedures Manual, Version 4 (Nov 2000) and Version 5 (March 2003). Genentech should provide ECOG Policy and Standard Procedures Manual for review.
17. CSR E2100, Section 6, page 20 and section 16.1.8, page 835: Each cooperative group conducted audits of its participating sites using policies and procedures modeled after guidance documents. Genentech should provide audit documentation from all cooperative groups for the investigational sites involved in E2100 study.
18. The data contained in this submission does not support a broad labeling claim for use of bevacizumab in combination with the drug class taxane-based chemotherapy, as proposed by the applicant. Genentech will need to conduct additional study (ies) to establish the clinical effectiveness of bevacizumab in combination with other taxanes alone and in combination with other chemotherapies.

III. Conclusion

The information and data submitted to support this sBLA are inadequate for final approval action due to the deficiencies outlined above.

Medical Officer's Consultative Review Memorandum

sBLA: 125085/91
Sponsor: Genentech
Product: Bevacizumab (Avastin)
Consultant: Lee Pai-Scherf, MD, OODP/DBOP
Reviewer: Barbara A. Stinson, DO, DMIHP *BS*
Through: Dwaine Rieves, MD, Deputy Director, DMIHP *DR* / 9-8-06
George Mills, Director, DMIHP *GM* 9/10/06
Today's date: August 30, 2006

I. Overview:

This consultation was requested to review the Independent Radiology Review Charter (IRC) submitted for an audit of a phase 3 clinical protocol titled "A Randomized Phase III Trial of Paclitaxel versus Paclitaxel plus Bevacizumab (rhuMab VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer." This sBLA is based on Protocol E2100 sponsored by NCI and ECOG (Eastern Cooperative Oncology Group). The sponsor, Genentech, has contracted RadPharm to provide a retrospective independent confirmation of the selected CT and MRI exams for selected subjects that were enrolled in this study.

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

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

Each cycle was repeated every 4 weeks until disease progression or unacceptable toxicity.

The primary objective was to evaluate the efficacy of bevacizumab plus paclitaxel compared with paclitaxel in patients with chemotherapy-naïve metastatic breast cancer as measured by progression-free survival. The secondary objectives were to compare the objective response rate, duration of response, and overall survival of paclitaxel to that of the combination of paclitaxel plus bevacizumab.

The tumor assessment schedule for imaging is duplicated on the following page, (taken from the RadPharm Procedures Document, page 17, dated 14Aug2006).

Exam	Pre-Study (Within 4 weeks before randomization)	Every 3 Cycles	Off- Treatment Follow-Up¹
Tumor Assessment	R	R	R

R: Required. "Scans or X-Rays" were required to document measurable and non-measurable disease.

¹: Follow-up after subject discontinues protocol therapy, every 3 months if subject is < 2 years from study entry; every 6 months if subject is 2-5 years from study entry.

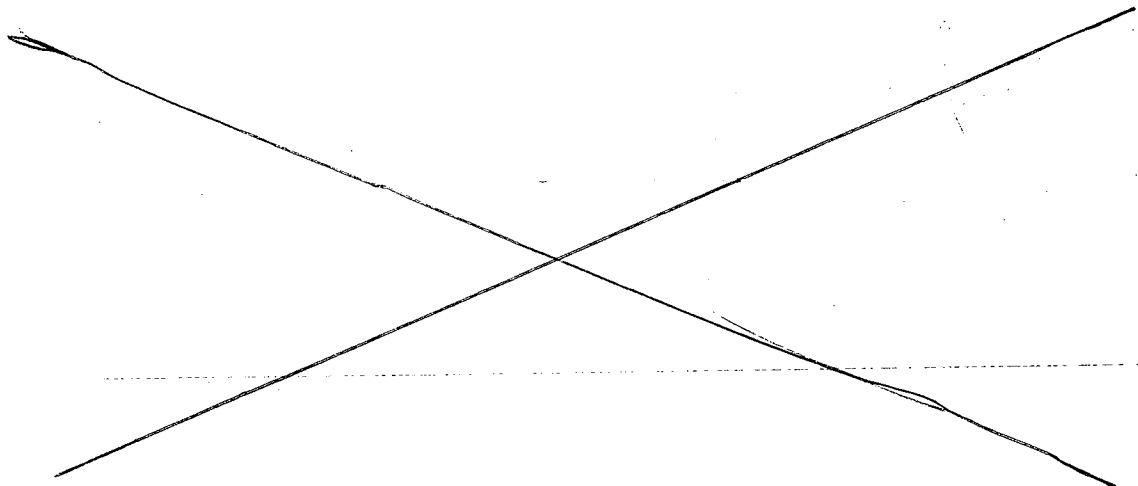
II. FDA DMIHP Consultant's findings:

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

Following discussion with the DBOP team, we concur that the use of the RECIST criteria as they were used by the site investigators is a useful goal. Hence, we concur that the sponsor should revise the draft charter in order to duplicate the site investigator's radiographic outcome assessment criteria. These items were discussed in a telephone conversation between the FDA and the sponsor on September 5, 2006.

III. Summary of Independent Radiology Review Process

IMAGING HANDLING



b(4)

b(4)

10 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125085 / S-091

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: [REDACTED] 1-25-08

Drug Name: Avastin (bevacizumab)

Indication(s): First line treatment for locally recurrent or metastatic breast cancer

Applicant: Genentech Inc.

Date(s): Submitted on 8/23/2007, PDUFA date 2/23/2008

Review Priority: Priority

Biometrics Division: Division of Biometrics V (HFD-711)

Statistical Reviewer: Dr. Laura Lu, Ph.D

Concurring Reviewers: Dr. Mark Rothmann, Ph.D, Team Leader
Dr. Aloka Chakravarty, Ph.D, Division Director

Medical Division: Division of Biological Oncology Products (HFD-107)

Clinical Team: Dr. Lee Pai-Scherf, MD, Medical Reviewer
Dr. Pat Keegan, MD, Division Director

Project Manager: Ms. Sharon Sickafuse

Keywords: Survival analysis, missing value, sensitivity analyses, discordance between radiologists in assessment of radiographic scan

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This reviewer's evaluation of the Phase III Study E2100 supports the conclusion that the addition of bevacizumab to paclitaxel as a first line treatment delays time to progression or early death (death within 84 days of the last protocol therapy) in patients with locally recurrent or metastatic breast cancer. However, Study E2100 failed to show an effect on overall survival (OS).

Additionally, the magnitude of the treatment effect on progression free survival (PFS) is not certain. Our confidence in the estimated 5.5 month improvement in median duration of PFS is limited by the following factors:

- Genentech was unable to obtain scans for 10% of patients.
- There are a large percentage of patients (34%) who were not followed until an independent review facility (IRF)-determined PFS event or until the end of study.
- The lack of reliability in determination of radiological disease progression and the date of progression between independent radiologists and between independent radiologists and study investigators.

Study AVF2119g failed to indicate advantages in PFS (HR = 0.98) and OS (HR = 1.08) when adding bevacizumab to capecitabine (CAP) as a second line treatment of metastatic breast cancer.

1.2 Brief Overview of Clinical Studies

BLA 215085/91 was submitted for the approval of Avastin (bevacizumab), in combination with paclitaxel, for first-line treatment of patient's locally recurrent or metastatic breast cancer. A Phase III trial (E2100) is the primary trial in support of the proposed indication. Another Phase III study (AVF2119g) for bevacizumab in combination with capecitabine used in the second line setting was also submitted.

The E2100 study is an open-label, randomized trial with 722 (354 in paclitaxel (PAC) arm, 368 in paclitaxel plus bevacizumab (PAC/BEV) arm) patients who have not received prior chemotherapy for their locally recurrent or metastatic breast cancer. Most of the patients (88%) were from US. The primary efficacy endpoint is PFS adjudicated by a blinded IRF. Secondary endpoints are overall survival, objective response rate, duration of objective response, and Quality of life (QoL). The study is sponsored by the National Cancer Institute (NCI) and conducted by Eastern Cooperative Oncology Group (ECOG).

AVF2119g is a multicenter, open-label, randomized study evaluating the efficacy, safety, and pharmacokinetics of bevacizumab, in combination with capecitabine (CAP) in patients with previously treated metastatic breast cancer. The primary endpoint of the study was progression

free survival as determined by IRF assessment. The secondary endpoints were objective response, overall survival, duration of objective response, and time to deterioration in QOL. The study was conducted in 96 study centers in the US from November 2000 to September 2002.

1.3 Statistical Issues and Findings

1. The sponsor's analyses had demonstrated a statistically significant result in PFS, but failed to show an advantage in OS. Also, FDA's confidence on the magnitude of the treatment effect (estimated 5.5 months' prolongation in median time to PFS) is affected by the following issues:

a. The estimated treatment effect in PFS is sensitive to different assumptions on missing value and lost-to-follow-up.

The primary analysis for PFS based on IRF assessment shows that the PAC/BEV arm had an estimated 5.5 month advantage over PAC arm in median duration of PFS. However, this 5.5 months advantage may not be reliable because Genentech was unable to collect scans for 10% of the study population and 247 (34%) of the patients were not followed until an IRF-determined PFS event or the end of study.

To assess the robustness of the magnitude of the PFS result in the presence of missing value and lost-to-follow-up, several sensitivity analyses were conducted by FDA with different assumptions for the outcome of missing value and lost-to-follow-up. The magnitude of the PFS result is sensitive to the different assumptions. The estimated difference in median duration of PFS varies from 0.4 to 4.1 months in these analyses (See Table 8 in Section 3.1.5. for detailed results).

b. There is a substantial discordance between IRF radiologists and between IRF and ECOG radiologists in PFS determination.

In order to assess the reliability of the radiologically-based, tumor-related endpoints, the consistency was evaluated between the two IRF radiologists, that working independently but reviewing the same information, in regarding the presence of disease progression and the data of progression. Among the 649 patients with scans available for IRF review, there were 217 patients (33%) for whom the two radiologists reached different conclusions regarding disease progression status or date of disease progression.

The discordance between IRF radiologists and ECOG radiologists in PFS determination was also evaluated. Across the entire study population, IRF and ECOG radiologists were not in agreement in 368 (51%) patients in either PFS status or PFS date.

FDA continues to gain experience regarding the reliability of radiologically-determined disease progression and at this time does not have sufficient experience to say whether the 33% rate of discordance between the IRF radiologists or the 51% rate of discordance between the IRF and ECOG radiologists are unusual. However, the level of discordance suggests a lack of reliability in the measurement of a given patient's PFS.

2. Study AVF2119g failed to indicate advantages in PFS (HR = 0.98) and OS (HR = 1.08) when adding bevacizumab to capecitabine (CAP) as a second line treatment of metastatic breast cancer. For further details see section 3.1.2.

2. INTRODUCTION

2.1 Overview

BLA 215085/91 was submitted for the approval of bevacizumab, in combination with paclitaxel, for first-line treatment of patient's locally recurrent or metastatic breast cancer. A Phase III trial (E2100) is submitted in support of the proposed indication.

The E2100 study is an open-label, randomized trial with 722 (354 in PAC arm, 368 in PAC/BEV arm) patients who have not received prior chemotherapy for their locally recurrent or metastatic breast cancer. Most of the patients (88%) were from the United States. The primary efficacy endpoint was PFS adjudicated by a blinded IRF. Secondary endpoints were overall survival, objective response rate, duration of objective response, and QoL. The study was sponsored by the National Cancer Institute (NCI) and conducted by Eastern Cooperative Oncology Group (ECOG).

This BLA supplement was originally submitted in May, 2006. After reviewing the information provided in the BLA supplement, FDA determined that the submission was inadequate to support a final approval action. FDA issued a complete review (CR) letter in September, 2006. In this letter, FDA stated that the dataset submitted was incomplete, without a data cutoff date for efficacy and safety. FDA also reiterated the need for an independent radiology review of the progression events in a subset of patients, given the subjective nature of the PFS endpoint and the open-label design of the study. Reference is made to the CR letter dated on 9/8/2006 for more detailed FDA comments. After a discussion with FDA in November 1996, Genentech agreed to provide complete and cleaned data with data cutoff date 2/9/2005 for efficacy evaluation. Genentech also agreed to set up an independent review facility to conduct an independent and blinded review of all 722 patients to verify the efficacy results. Genentech was asked to submit the updated survival data at the time of resubmission. In August 2007, BLA 125081/91 was resubmitted for FDA review.

FDA was particularly concerned about the incompleteness of the efficacy and safety data of Study E2100. The incompleteness of data is reflected in the fact that additional PFS events were added with each new ECOG or Genentech analyses with the same data cutoff 2/9/2005. In April, 2005, ECOG conducted their first interim analysis with data cutoff 2/9/2005. In this analysis, 260 PFS events were found. In May, 2005, ECOG presented another analysis in the meeting of American Society of Clinical Oncology with the same data cutoff 2/9/2005. In this analysis, 355 PFS events were found. In the BLA submitted in May 2006, Genentech reported 395 PFS events with a data cutoff date of 4/14/2005. In the current BLA submitted on August, 2007, 445 PFS events were found by the data cutoff date of 2/9/2005. These data were deemed as complete and cleaned by Genentech.

2.2 Data Sources

Efficacy evaluation in this BLA was mainly based on three electronic datasets: 'IRFPAT.xpt', a derived efficacy dataset based on IRF assessment; 'PAT.xpt', a derived efficacy dataset based on ECOG assessment; 'RESFIN2.xpt', a raw dataset based on IRF tumor assessment; and 'FLAGPAT.spt', a derived dataset compares tumor assessments between IRF radiologists. 'IRFPAT.xpt' and 'PAT.xpt' can be accessed at '\\cbsap58\M\EDR Submissions\2006 BLA\DCC60002991\BL125085-91.018\crt\datasets\e2100'. 'RESFIN2.xpt' and 'FLAGPAT.xpt' can be accessed at '\\cbsap58\M\EDR Submissions\2006 BLA\DCC60002991\BL125085-91.033\crt\datasets\e2100-irf'.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study E2100

3.1.1.1 Study Design and Endpoints

Study E2100 is an open-label, Phase III, multicenter, randomized, controlled trial of patients who had not previously received chemotherapy for their locally recurrent or metastatic breast cancer. Patients were randomized 1:1 to receive either:

- **Arm A** Paclitaxel 90mg/m² iv over 1 hr every wk for 3 wks followed by 1 wk rest
Bevacizumab 10 mg/kg following paclitaxel on wks 1 and 3 of every cycle
- **Arm B** Paclitaxel 90mg/m² iv over 1 hr every wk for 3 wks followed by 1 wk rest

Randomization was stratified according to disease-free interval (≤ 24 , > 24 months), number of metastatic sites (< 3 , ≥ 3), prior adjuvant chemotherapy (yes, no) and ER status (positive, negative, and unknown).

Treatment was given every 4 weeks until disease progression, unacceptable toxicity, or death due to any cause. Tumor assessment by scans or x-ray was performed at baseline, every 3 cycles while the patients were on protocol therapy. Patients who discontinued protocol therapy were to be assessed for tumor progression and non-protocol cancer therapy until disease progression and toxicity every 3 months for up to 2 years from randomization and every 6 months from 2 to 5 years from randomization.

The primary endpoint of this study was PFS and the secondary endpoints were OS, response rate, duration of response and QoL as assessed by FACT-B questionnaire. Per agreement with Genentech (FDA meeting of November 2, 2006), all tumor assessment data including pertinent clinical information were to be retrospectively reviewed by a blinded IRF.

PFS was defined to be the time from randomization to disease progression as determined by the IRF, or death within 84 days of the last study treatment. The following censoring rules were applied:

1. If no PD or death by efficacy data cutoff date, censored at the date of last tumor assessment before the cutoff date
2. If dead before efficacy data cutoff date, but after 84 days following last treatment, censored at the last tumor evaluation date
3. If NTP prior to documented PD, censored at the time of last tumor assessment prior NTP
4. If no scans or clinical info submitted to IRF, censored at the randomization.

The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all patients who were randomized to protocol therapy.

For the primary endpoint PFS, A total of 546 PFS events are needed to provide 85% power to detect a 33 % increase in median PFS from 6 months in Arm B to 8 months in Arm A with a one-sided Type I error rate of 0.025. Two interim analyses for efficacy were planned in the protocol at 270 and 425 events using O'Brien-Fleming boundary for the adjustment of Type I error rate. PFS was analyzed by the stratified Cox regression method with the pre-randomization stratification factors as stratification factors for the analysis.

A final analysis for OS was planned after 481 deaths have occurred, which provides 80% power at an Avastin vs. no Avastin hazard ratio of 0.78 with a one-sided Type I error rate of 0.025. This hazard ratio corresponds with a 29% improvement in median OS from 24 months to 31 months for survival times that have an exponential distribution. OS was analyzed the same way as that for PFS. The primary analysis for objective response rate was performed using Cochran-Mantel-Haenszel test with the pre-randomization stratification factors as stratification factors only patients with measurable disease at baseline.

3.1.1.2. Patient Disposition

Between 21 December 2001 and 26 May 2004, 722 patients were randomized in a 1:1 ratio to one of two treatment arms: 354 patients to the paclitaxel alone arm and 368 patients to the paclitaxel + bevacizumab arm. Table 1 summarizes patient disposition and reason for treatment discontinuation based on all data contained in the ECOG database as of the safety data cutoff of 9 August 2005. A total of 711 patients (98.5%) received protocol therapy; 10 patients never initiated protocol therapy, and this information was unknown for 1 patient. Of the 711 treated patients, 664 patients (92.0%) had discontinued protocol therapy. More patients had not yet discontinued protocol therapy in the paclitaxel + bevacizumab arm compared with the paclitaxel alone arm (39 vs. 8 patients). Information regarding patient disposition are summarized in Table 1.

Table 1. Patient Disposition and Reason for Protocol Therapy Discontinuation

Status and Reason for Protocol Therapy Discontinuation	PAC (n = 354)	PAC/BEV (n = 368)	Total (n = 722)
Treated ^a	346 (97.7%)	365 (99.2%)	711 (98.5%)
Not known to have discontinued protocol therapy	8 (2.3%)	39 (10.6%)	47 (6.5%)
Discontinued protocol therapy	338 (95.5%)	326 (88.6%)	664 (92.0%)
Treatment completed per protocol ^b	11 (3.1%)	17 (4.6%)	28 (3.9%)
Disease progression/relapse during active treatment	193 (54.5%)	167 (45.4%)	360 (49.9%)
Toxicity/side effects/complications	68 (19.2%)	74 (20.1%)	142 (19.7%)
Death on study	5 (1.4%)	6 (1.6%)	11 (1.5%)
Patient withdrawal or refusal	30 (8.5%)	27 (7.3%)	57 (7.9%)
Alternative therapy	6 (1.7%)	8 (2.2%)	14 (1.9%)
Other complicating disease	1 (0.3%)	4 (1.1%)	5 (0.7%)
Other ^c	24 (6.8%)	23 (6.3%)	47 (6.5%)
Not treated	8 (2.3%)	2 (0.5%)	10 (1.4%)
Patient not eligible	1 (0.3%)	1 (0.3%)	2 (0.3%)
Patient refused treatment	2 (0.6%)	0 (0.0%)	2 (0.3%)
Disease progression before active treatment	1 (0.3%)	0 (0.0%)	1 (0.1%)
Other	4 (1.1%)	1 (0.3%)	5 (0.7%)
Unknown	0 (0.0%)	1 (0.3%)	1 (0.1%)

Note: Data are based on a cutoff date of 9 August 2005.

^a Treated as randomized; therefore, the numbers are different from the safety population.

^b Reflects the number of patients who completed 18 months of therapy, the maximum duration of therapy allowed prior to removal of this requirement in the sixth protocol amendment.

^c Most frequent reasons in the "Other" category appear to include suspicion of progression, voluntary treatment break, or physician discretion.

3.1.1.3. Demographic and Baseline Characteristics

A total of 722 patients were randomized to the study. Patient characteristics of the ITT population are summarized in Table 2. Randomization was in general well balanced, with the exception of presence of measurable disease at baseline (77.1% in the PAC arm versus 68.5% in the PAC/BEV arm).

Table 2. Patient Demographics, Tumor Characteristics and Prior Therapy

	PAC N = 354	PAC/BEV N= 368	TOTAL N=722
Demographics			
Gender: Female	350 (98.9)	366 (99.5)	716 (99.2)
Age: median (range)	55 (27-85)	56 (29-84)	55 (27-85)
Race white	266 (75)	284 (77.2)	550 (76.2)
black	35 (9.9)	34 (9.2)	69 (9.6)
others	26 (7.4)	23 (6.1)	49 (13.5)
Menopausal status			
Pre	55 (15.5)	63 (17.1)	118 (16.3)
Post	204 (57.6)	195 (53.0)	399 (55.3)
Tumor Characteristics			
Metastatic	349 (98.9)	360 (97.8)	709 (98.3)
Locally recurrent	4 (1.1)	8 (2.2)	12 (1.7)
No. of involved sites			
< 3	184 (52)	208 (56.5)	392 (54.3)
≥ 3	170 (48)	160 (43.5)	330 (45.7)
Most common sites of involvement			
Bone	192 (54.4)	201 (54.6)	393 (54.5)
Liver	157 (44.5)	144 (39.1)	301 (41.7)
Lung	146 (41.4)	153 (41.6)	299 (41.5)
Local-regional	116 (32.9)	121 (32.9)	237 (32.9)
Distant nodes	97 (27.5)	103 (28.0)	200 (27.7)
Bone only	27 (7.6)	36 (9.8)	63 (8.7)
ER status			
Positive	127 (35.9)	138 (37.5)	265 (36.7)
Negative	233 (63.0)	223 (60.6)	446 (61.8)
Unknown	4 (1.1%)	7 (1.9)	11 (1.5)
HER2 status (FISH/IHC)			
Negative	316 (89.3)	334 (90.8)	650 (90)
Positive	6 (1.7)	9 (2.4)	15 (2.1)
Unknown	32 (9.0)	25 (0.8)	57 (7.9)
Disease-free interval			
≤ 24 months	146 (41.2)	150 (40.8)	296 (41.0)
> 24 months	208 (58.8)	218 (59.2)	426 (59.0)
Measurable disease at baseline			
Yes	273 (77.1)	252 (68.5)	525 (72.7)
No	81 (22.9)	116 (31.5)	197 (27.3)
Hormonal therapy			
Adjuvant	175 (49.4)	168 (45.7)	343 (47.5)
Metastatic	128 (36.2)	134 (36.4)	262 (36.3)
Chemotherapy			
Adjuvant	231 (65.3)	244 (66.3)	475 (65.8)
Metastatic	1 (0.3)	1 (0.3)	2 (0.3)
Prior taxane	68 (19.2)	74 (20.1)	142 (19.7)
Prior anthracycline	180 (50.8)	184 (50.0)	364 (50.4)

3.1.1.4. Efficacy Results

Progression Free Survival

Progression Free Survival was adjudicated by a blinded IRF. Scans were retrospectively collected by Genentech and forwarded to the IRF for determination of disease progression events and for objective tumor response assessment. Genentech was unable to collect scans for 10% of the study population. The tumor assessments for these patients were based on clinical evaluation.

The median PFS time was 11.3 months for the PAC/BEV arm and 5.8 months for the PAC arm, (HR = 0.48, $p < 0.0001$). One hundred eighty four patients (52%) in the PAC arm and 173 patients (47%) in the PAC/BEV arm had an event. Detailed results are presented in Table 3. The Kaplan-Meier curves for PFS are displayed in Figure 1.

Table 3. PFS Results based on IRF Assessments

	PAC (N=354)	PAC/BEV (N=368)
No. of patients with an event ^a (%)	184 (52.0)	173 (47.0)
Censored (%)	170 (48.0)	195 (53.0)
Earliest contributing event		
Disease Progression	166	158
On-Study death ^b	18	15
Median (month)	5.8	11.3
HR ^c	0.48	
95% CI	(0.38, 0.60)	
p-value ^d	<0.0001	

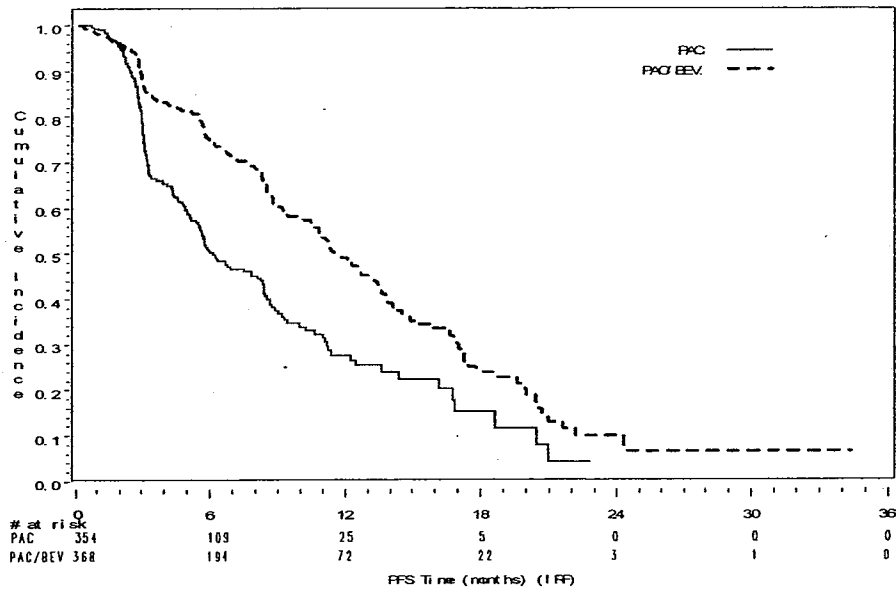
^a PFS events with data cutoff date of 2/9/05

^b Death within 84 days of the last protocol therapy

^c HR was estimated by the stratified Cox regression method. The strata were disease-free interval (≤ 24 , > 24 months), number of metastatic sites (≤ 3 , > 3), adjuvant chemotherapy (yes, no), and ER status (positive, negative, or unknown).

^d p-value by the stratified Cox regression method

Figure 1. Progression-Free Survival



An exploratory analysis for PFS based on ECOG assessment was conducted. The median duration of PFS was 11.4 months for the PAC/BEV arm and 5.8 months for the PAC arm, (HR = 0.42, $p < 0.0001$). Two hundred and forty-four patients (68.9%) in the PAC arm and 201 patients (54.6%) in the PAC/BEV arm had an event.

The sponsor also conducted sensitivity analysis in assessing the robustness of PFS results. The results of these sensitivity analyses are presented in Table 4 below. These results are consistent with that of the primary analyses in general. The FDA reviewer also conducted additional sensitivity analyses. The results of these additional analyses are discussed in Section 3.1.5.

Table 4. Results of Sponsor Conducted Sensitivity Analyses

IRF-Assessed PFS Analysis	Hazard Ratio	(95% CI)
Primary analysis	0.48	(0.39, 0.61)
PFS analysis based on missing tumor assessments ^a	0.48	(0.39, 0.61)
PFS analysis with non-protocol therapy (NPT) use and early discontinuation as PD events ^b	0.50	(0.41, 0.59)
Worst-case analysis ^c	0.78	(0.64, 0.95)
PFS analysis without censoring for anti-tumor NPT	0.57	(0.46, 0.71)
PFS analysis including deaths observed after completion of tumor assessments ^d	0.48	(0.38, 0.61)
PFS analysis including all deaths before 2/9/05 ^e	0.54	(0.44, 0.66)

a: Patients with a PD who missed the evaluation immediately prior to the PD had their PD date replaced by the date of the first missed tumor assessment.

b: NPT and early discontinuation (no tumor evaluation within 168 days of data cutoff date) were considered PD events.

c: NPT and early discontinuation were considered PD events for patients in the PAC/BEV arm only.

d: Deaths within 84 days of last tumor assessment were considered.

e: All death before 2/9/05 were considered.

SURVIVAL

The overall survival results are shown in Table 5. The cutoff date for overall survival analysis is 10/21/05 when a total of 481 deaths had occurred (238 (67.2%) in the PAC arm and 243 (66.0%) in the PAC/BEV arm). There was no statistically significant difference in the median OS PAC/BEV arm (26.5 months) compared to the PAC arm (24.8 months) with $p=0.1374$. The hazard ratio was 0.87. The Kaplan-Meier curves for OS are displayed in Figure 2.

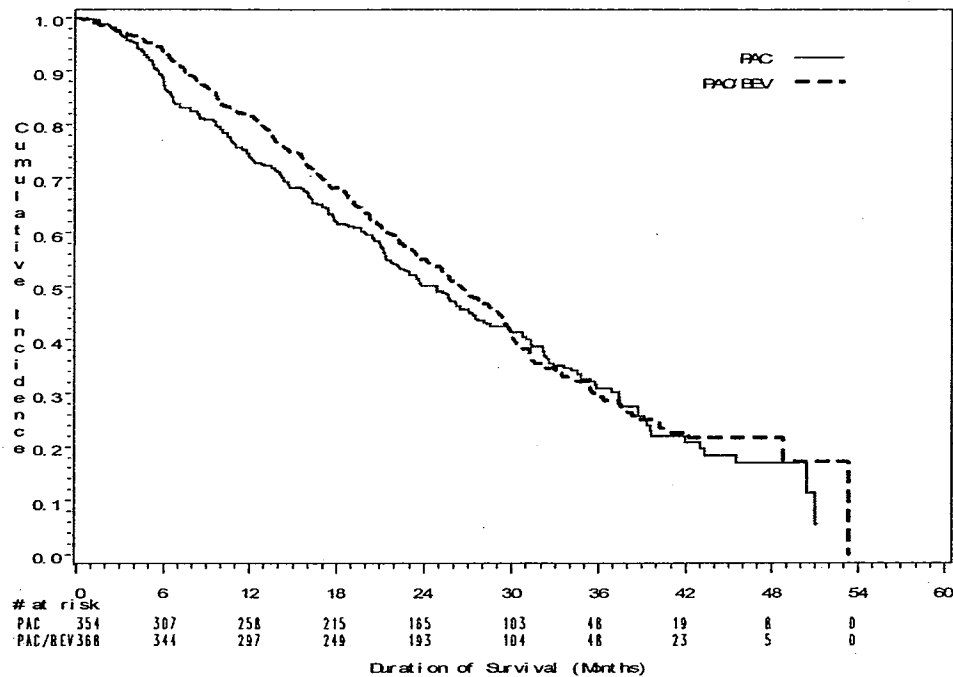
Table 5. OS Results Based on IRF Assessments

	PAC (n = 354)	PAC/BEV (n = 368)
No. of patients who died ^a (%)	238 (67.2%)	243 (66.0%)
Median (month)	24.8	26.5
HR ^b (relative to PAC)	0.869	
95% CI ^b	(0.722, 1.046)	
p-value ^b	0.1374	

a: Death by 10/21/05.

b: Analyses by the stratified Cox method. The factors are disease-free interval (≤ 24 , ≥ 24 months), number of metastatic sites (< 3 , ≥ 3), adjuvant chemotherapy (yes, no), and ER status (positive, negative, or unknown).

Figure 2. Overall Survival



Objective Tumor Response

IRF assessed objective tumor response using RECIST criteria are shown in Table 6. Overall response rate was significantly higher in the PAC/BEV arm when compare to PAC alone (48.9 % versus 22.2 %). Among the patients who achieved an objective response, the median objective response was 9.7 months for the PAC arm and 9.4 months for the PAC/BEV arm.

Table 6. Objective Response

	PAC N = 243	PAC/BEV N = 229
No. of patients with objective response (%)	54 (22.2%)	112 (48.9%)
Complete response	0 (0.0%)	0 (0.0%)
Partial response	54 (22.2%)	112 (48.9%)
Difference in response rate (%)	26.7%	
95% CI ^a	(18.4%, 35.0%)	
p-value ^b	< 0.0001	
Median duration of response among responders (month)	9.7	9.4

a: by the standard normal approximation.

b: Cochran-Mantel-Haenszel test stratified by disease-free interval (≤ 24 , >24 months), number of metastatic sites (<3 , ≥ 3), adjuvant chemotherapy (yes, no), and ER status (positive, negative, or unknown).

Quality of Life

Quality of life was assessed by ECOG using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. The primary analysis for QOL was the change in the Trial Outcome Index (TOI) score from baseline to Week 17 for patients in arm A and B. In this primary analysis, patients with missing score following progressed or death were assigned 0, the worst score. If QOL scores were missing for any reason other than disease progression or death, they were not imputed and the patient was not included in the analysis. Only 572 patients were included in the analysis for change from baseline at Week 17 in TOI due to missing value. Although the mean deterioration in QOL from baseline to Week 17 was statistically significant in favor of the PAC/BEV arm (see Table 7 below), clinical significance of this finding is unclear. Most significantly, the quality of life assessment can not be used to support an Avastin label expansion because the study was open-labeled, and no information on concurrent medications was collected.

Table 7. Quality-of-Life Change from Baseline TOI

	PAC			PAC/BEV			p-value
	n	Mean	SD	n	Mean	SD	
Baseline	270	63.8	14.4	302	65.4	13.9	
Week 17	270	51.2	27.1	302	58.8	21.0	
Change from baseline	270	- 12.7	24.5	302	- 6.6	18.5	0.0069

Note: The p-value was from the Wilcoxon rank-sum test. Missing QOL scores for patients who had progressive disease per the IRF or who died prior to Week 17 were replaced with 0 (the worst QOL score). If QOL scores were missing after imputation at Week 17, the patient was not included in this table for the respective timepoint.

3.1.1.5. Reviewer's Comments

1. The robustness of treatment effect in PFS in presence of missing value and lost-to-follow-up

The primary analysis for PFS based on IRF assessment show that the PAC/BEV arm had an estimated 5.5 month advantage over PAC arm in median duration of PFS. However, this 5.5 months advantage may not be reliable due to that facts that Genentech was unable to collect scans for 10% of the study population and 247 (34%) of the patients were not followed until an IRF-determined PFS event or the end of study (no tumor assessments within 3 months of the data cutoff date 2/9/2005). Among these 34% of patients lost to follow-up, 6% were due to no scans or pertinent clinical information, 11% were due to use of NPT, 12% were due to censoring by IRF for those patients who were determined as PDs by ECOG but not by IRF, and 5% were without a clear reason for lost-to-follow-up. Although 23% (11%+12%) were followed

accordingly to the protocol, they do affect the confidence on the reliability of the PFS comparison. Censoring these patients' PFS is probably informative.

The sponsor reported 37% of lost-to-follow-up in the Oncology Drug Advisory Committee meeting. The sponsor's result was based on the difference between the PFS event (or censoring) date and the data cutoff date. If the difference between the PFS date and the efficacy data cutoff date 2/9/05 is longer than 3 months, then the patient was counted as a lost-to-follow-up. The difference of 3% between FDA and sponsor's results are due to the inclusion, by the sponsor, of those patients who took NPT 3 months before the data cutoff date (therefore, PFS was censored at the NPT use) but still had tumor assessment data within 3 months of data cutoff date as lost-to-follow-ups.

To assess the robustness of the magnitude of PFS result with the presence of missing value and lost-to-follow-up, the following sensitivity analyses were conducted by FDA with data cutoff date of 2/9/2005:

1. Time to progression is time to the earliest of ECOG or IRF PFS event.
2. In the PAC arm, time to progression is the earliest of time to first PD event, time to death within 84 days of last protocol therapy; In the PAC/BEV arm, time to progression is the earliest time to first PD event, time to death within 84 days of last protocol therapy, or time to lost-to-follow-up plus 1 day. This analysis is also referred as the FDA Worst Case Analysis #1.
3. In the PAC arm, time to progression is the earliest of time to first PD event, time to death within 84 days of last protocol therapy; In the PAC/BEV arm, time to progression is the earliest time to first PD event, time to death within 84 days of last protocol therapy, time to lost-to-follow-up plus 1 day, time to the last clinical assessment plus 1 day for those patients without scan for IRF but with had any clinical assessment results, or 1 day for those patients without scan for IRF and without any clinical assessment results. This analysis is also referred as the Worst Case Analysis #2.

The results of these sensitivity analyses are displayed in Table 8 below. The results of the primary analysis were displayed in the first row for comparison. The estimated difference in median to PFS varies from 0.4 to 4.1 months in these analyses.

Table 8. Sensitivity Analyses for PFS

	Median (month)		Difference in Median	Hazard Ratio
	PAC	PAC/BEV		
Primary analysis-IRF	5.8	11.3	5.5	0.48 (p<0.0001)
Time to earliest PFS event (IRF or ECOG)	4.9	9.0	4.1	0.46 (p<0.0001)
FDA worst case 1 (LTFU as events in BEV arm only)	5.8	7.4	1.6	0.89 (p=0.26)
FDA worst case 2 (no scan, LTFU as events in BEV arm only)	5.8	6.2	0.4	0.99 (p=0.88)

2. Discordance between IRF radiologists in PFS Determination

There were two IRF radiologists who read all available scans for each clinical trial subject in order to determine the presence and date of radiographic disease progression. These readings were performed independently and without knowledge of the treatment which the patient received.

If the results of the two readings were discordant, a third radiologist performed an additional reading to arrive at a final adjudicated interpretation of the radiology results. In addition, a medical oncologist reviewed clinical records and other information to make a determination of disease progression based on clinical, or non-radiological, criteria.

In order to assess the reliability of the radiologically-based, tumor-related endpoints, FDA evaluated the lack of consistency between the two IRF radiologists in regarding the presence of disease progression and the data of progression. There were a total of 649 patients for whom radiologic scans were provided to the IRF. Among these 649 patients, there were 295 patients (45.5%) where the two radiologists did not agree on the status of disease progression or of tumor response or in whom they identified a different date for disease progression or onset of response (see Table 9). The discordance rates between the two radiologists were similar between the two treatment arms.

Table 9. Lack of Consistency between the IRF Radiologists in Scan Reading

	N	No. Patients Adjudicated for Discordant Response or PD Status/Date
Patients with Scan	649	295 (45.5%)
PAC	319	138 (43.3%)
PAC/BEV	330	157 (47.6%)

This reviewer also conducted an assessment of the lack of consistency with regard to the two IRF radiologists for disease progression events. Among the 649 patients with scans available for IRF review, there were 217 patients, which account for 33.4% of the study population where the two radiologists reached different conclusions regarding disease progression status or date of disease progression. The level of disagreement on disease status or date of disease progression was higher among patients with a final IRF-determination of disease progression. Among the 278 patients with a final IRF-determination of disease progression, the two radiologists did not agree on the disease progression status or date of progression in 45.0%. Among the 371 patients that had no evidence of radiographic progression by the final IRF assessment, the two radiologists did not agree on disease progression status in 24.8% of these patients. These results are displayed in Table 10 below.

Table 10. Lack of Consistency between IRF Radiologists for PD Status or Date

	N	No. of Patients with Discordant PD Status or Date (%)
Patients with Scan	649	217 (33.4)
Radiographic PD	278	125 (45.0)
No Radiographic PD	371	92 (24.8)

FDA continues to gain experience regarding the reliability of radiologically-determined disease progression and at this time does not have sufficient experience to say whether the 33.4% rate of discordance between two radiologists is unusual. However, the level of discordance suggests a lack of reliability in the measurement of a given patient's PFS, particularly for patients with disease progression events.

3. Discordance between IRF radiologists in PFS Determination

The discordance between IRF and ECOG determination of PFS status (event/ no event) was assessed. In looking at the direction of the disagreements, we consider whether the investigators consistently or generally favor the experimental arm over the control arm.

In Table 11, we provide the discordance rate between the IRF and ECOG investigators for disease progression status by treatment arm. In the first column, 3.4% of patients in the PAC arm and 8.4% patients in the PAC/BEV arm were determined to have disease progression by the IRF but no evidence of disease progression by ECOG investigators. Therefore, the discordance rates are slightly different for the two study arms, with the difference favoring the PAC/Bev arm over the PAC arm in ECOG investigator-determined assessment of PFS.

Table 11. Discordance between IRF and ECOG in PFS Event Status

Treatment Arm	No. of discordance (%)	
	IRF progressed ECOG censored	IRF censored ECOG progressed
PAC	12 (3.4)	72 (20.3)
PAC/BEV	31 (8.4)	59 (16.0)
Total	43 (6.0)	131 (18.1)

Besides the 174 patients whose PFS status were not agreed by ECOG and IRF, there were additional 197 patients whose PFS status were agreed by ECOG and IRF but the date of progression were not agreed by ECOG and IRF. Therefore, a total of 368 patients (51%) were not agreed by ECOG and IRF on either PFS status or date of progression.

4. Power for the overall survival analysis

At the oncology advisory committee meeting, the sponsor presented that the power for the overall survival analysis for a 3-month improvement in median overall survival is 25%. This assumes that the two medians are 24 months and 27 months, and also that the overall survival times are exponentially distributed. Under that assumption the Avastin vs. no Avastin hazard ratio is 0.89. However, the observed hazard ratio of 0.87 from the primary analysis went with an observed 1.7 months improvement in median overall survival. Therefore a hazard ratio less than 0.87 would seem to go with a 3 months improvement in median overall survival. From our calculations based on the observed results and a slightly crude model, an Avastin vs. no Avastin hazard ratio of 0.775 would seem to go with a 3 months improvement in median overall survival. This hazard ratio is approximately that hazard ratio that was used to power the analysis at 80% power. The power for the overall survival analysis for a 3-month improvement in median overall survival appears to be about 80%. Exponential distributions are easy to use and have been used to assist in the design of clinical trials, particularly to guide in determining anticipated timing of an event-driven analysis. However, it is important to note that human beings, cancer patients, do not have lifetimes or remaining lifetimes that are exponentially distributed. Exponential distributions have constant failure rates and are appropriate models for things that fail or die usually based on a sole random shock (e.g., light bulbs or electronic components) or for things that truly have "half-lives."

3.1.1.6. Efficacy Conclusion for Study E2100

This reviewer's evaluation of the Study E2100 supports the conclusion that bevacizumab treatment delays time to progression or early death. However, Study E2100 failed to show an effect on overall survival.

Additionally, the magnitude of the treatment effect on progression free survival is not certain. Our confidence in the estimated 5.5 month improvement in median duration of PFS is limited by the following factors:

- Genentech was unable to obtain scans for 10% of patients.
- There are a large percentage of patients (34%) who were not followed until an IRF-determined PFS event or until the end of study.
- The lack of reliability in determination of radiologic disease progression and the date of progression between independent radiologists and between independent radiologists and study investigators.

3.1.2 Summary Results of Study AVF2119g

AVF2119g is a multicenter, open-label, phase 3, randomized study evaluating the efficacy, safety, and pharmacokinetics of bevacizumab (BEV), in combination with capecitabine (CAP) in patients with previously treated metastatic breast cancer. Eligible patients were randomized 1:1 to receive CAP alone or CAP plus BEV (TP1). Randomization was stratified by ECOG PS

(0 or ≥ 1) and number of chemotherapy regimens for metastatic disease (0 or ≥ 1). Patients in the bevacizumab arm were eligible to continue bevacizumab therapy either alone or in combination with other chemotherapy regimens after disease progression (TP2).

The primary endpoint of the study was progression free survival as determined by IRF assessment. The secondary endpoints were objective response, overall survival, duration of objective response, and time to deterioration in QOL. The study was conducted in 96 study centers in the US from November 2000 to September 2002.

The study enrolled 462 patients, 230 patients in the capecitabine alone arm and 232 patients in the capecitabine plus bevacizumab arm. Randomization was in general, well balanced between the two arms. All patients were female, the mean age was 51.7 years (range 29 - 78), 15.6% of the patients did not receive prior chemotherapy for metastatic disease, and almost all patients received prior anthracycline and a taxane treatment, either in the adjuvant or metastatic settings.

The study failed to demonstrate a statistically significant effect on PFS and overall survival. The median PFS (Table 12) was 4.1 months in the capecitabine arm and 4.8 months in the capecitabine plus bevacizumab arm (log-rank p-value = 0.85, hazard ratio 0.98):

Table 12. Progression Free Survival (Study AVF2119g)

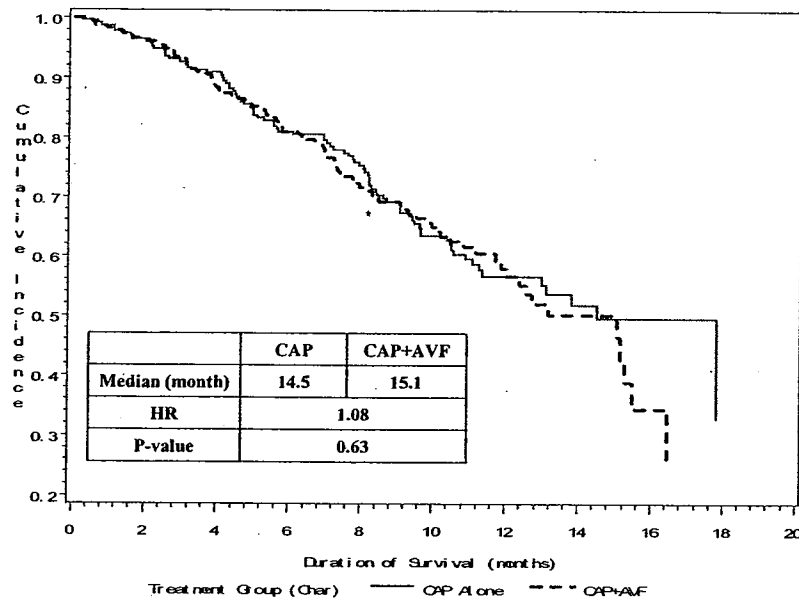
	Capecitabine (N=230)	Capecitabine + BEV (N=232)
Subjects with an event	126 (55%)	146 (63%)
Disease Progression	124 (54.1%)	143 (61.7%)
Death	2 (0.9%)	3 (1.3%)
Censored Subjects	104 (45%)	86 (37%)
Subject Censored at Day 1	27 (11.3%)	8 (3.4%)
Progression Free Survival (months)		
Median	4.17	4.86
95% CI	(3.71, 5.13)	(4.17, 5.52)
Stratified Analysis ^a		
Hazard Ratio ^b	-	0.98
95% CI	-	(0.77, 1.25)
p-value (log-rank)	-	0.857

^a Stratification by ECOG PS (0, 1), chemotherapy for metastatic disease (yes, no)

^b Relative to capecitabine alone

The median duration of survival (Figures 3) was 14.5 months in the capecitabine arm and 15.0 months in the capecitabine plus bevacizumab arm (log-rank p value = 0.62). The hazard ratio of 1.08 favored the control arm of capecitabine alone. The objective response rate was higher in the bevacizumab arm (19.8% vs. 9.1%).

Figure 3. Overall Survival (Study AVF2119g)



3.2 Evaluation of Safety

Please see the medical officer Dr. Lee Pai-Scherf's review in regards of safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Subgroup results on PFS and OS are analyzed for Study E2100 by gender, age and race. Detailed results based on Study E2100 data are displayed in Tables 13 and 14. The hazard ratios provided are for unadjusted analyses. The PFS analyses use the data that were used in the sponsor's primary analysis. The subgroup results for PFS are generally consistent with that of the primary analysis with hazard ratios below 1. The hazard ratios for survival in subgroup analyses are not consistently below or above 1.

Table 13. PFS Results by Gender, Race and Age

Baseline Risk Factor	Total n	# Events	PAC n	# Events	PAC/BEV n	# Events	Hazard Ratio	(95% CI)
All Patients	722	357	354	184	368	173	0.54	(0.44 - 0.67)
Age (yrs)								
< 40	59	37	32	20	27	17	0.54	(0.26 - 1.09)
40 - 64	496	243	239	121	257	122	0.51	(0.39 - 0.66)
≥65	167	77	83	43	84	34	0.67	(0.42 - 1.05)
Race								
White	550	268	266	136	284	132	0.54	(0.42 - 0.69)
Non-White	172	89	88	48	84	41	0.55	(0.36 - 0.86)

Table 14. OS Results by Gender, Race and Age

Baseline Risk Factor	Total n	# Deaths	PAC n	# Deaths	PAC/BEV n	# Deaths	Hazard Ratio	(95% CI)
All Patients	722	481	354	238	368	243	0.93	(0.78 - 1.11)
Age (yrs)								
< 40	59	38	32	20	27	18	1.06	(0.56 - 2.00)
40 - 64	496	326	239	169	257	157	0.77	(0.62 - 0.96)
≥ 65	167	117	83	49	84	68	1.55	(1.07 - 2.25)
Race								
White	550	377	266	186	284	191	0.91	(0.75 - 1.12)
Non-White	172	104	88	52	84	52	1.01	(0.68 - 1.48)

4.2 Other Special/Subgroup Populations

Results of other subgroup analyses for PFS and OS for Study E2100 were presented in Tables 15 and 16. The subgroup results for PFS are generally consistent with that of the primary analysis with hazard ratios below 1, except for the ER status 'unknown' group which had only 1 event in the PAC arm and 2 events in the PAC/BEV arm.

Table 15. PFS Results by Other Subgroups

Baseline Risk Factor	Total n	# Events	PAC n	# Events	PAC/BEV n	# Events	Hazard Ratio	(95% CI)
All Patients	722	357	354	184	368	173	0.54	(0.44 - 0.67)
Region								
North America	663	327	324	167	339	160	0.55	(0.44 - 0.68)
Rest of the World	59	30	30	17	29	13	0.43	(0.19 - 0.94)
Disease Status								
Locally recurrent	12	6	4	1	8	5	0.83	(0.09 - 8.04)
Metastatic	709	351	349	183	360	168	0.54	(0.44 - 0.67)
Disease-Free Interval (mo)								
≤24	296	163	146	81	150	82	0.58	(0.42 - 0.79)
< 24	426	194	208	103	218	91	0.50	(0.38 - 0.67)

ER Status									
Positive	446	211	223	103	223	108	0.59	(0.44 - 0.78)	
Negative	265	143	127	80	138	63	0.44	(0.31 - 0.61)	
Unknown	11	3	4	1	7	2	1.70	(0.15 - 19.07)	
ER/PR/HER2 combined									
Negative	232	125	110	67	122	58	0.49	(0.34 - 0.70)	
All others	490	232	244	117	246	115	0.57	(0.44 - 0.75)	
HER2 status									
Positive	15	10	6	6	9	4	0.00	(0.00 -)	
Negative	650	317	316	162	334	155	0.57	(0.45 - 0.71)	
Unknown	57	30	32	16	25	14	0.42	(0.19 - 0.93)	
Number of metastatic sites									
< 3	514	239	252	125	262	114	0.53	(0.41 - 0.69)	
≥3	208	118	102	59	106	59	0.56	(0.38 - 0.81)	
Measurable Disease at baseline									
Yes	472	248	243	125	229	123	0.66	(0.51 - 0.85)	
No	250	109	111	59	139	50	0.37	(0.25 - 0.54)	
SLD of target lesions – IRF									
≤Median	238	119	116	56	122	63	0.72	(0.50 - 1.03)	
> Median	234	129	127	69	107	60	0.63	(0.44 - 0.91)	
Prior adjuvant hormone therapy									
Yes	343	158	175	84	168	74	0.56	(0.41 - 0.77)	
No	379	199	179	100	200	99	0.52	(0.39 - 0.70)	
Metastatic/Recurrence hormone therapy									
Yes	262	121	128	61	134	60	0.53	(0.37 - 0.77)	
No	460	236	226	123	234	113	0.55	(0.43 - 0.72)	
Prior adjuvant chemotherapy									
Yes	475	232	231	121	244	111	0.47	(0.36 - 0.61)	
No	247	125	123	63	124	62	0.70	(0.49 - 1.01)	
Prior taxane therapy									
Yes	142	73	68	39	74	34	0.33	(0.20 - 0.54)	
No	580	284	286	145	294	139	0.60	(0.47 - 0.76)	
Prior anthracycline therapy									
Yes	364	183	180	97	184	86	0.53	(0.41 - 0.69)	
No	358	174	174	87	184	87	0.56	(0.38 - 0.81)	
Bone only									
Yes	63	18	27	10	36	8	0.28	(0.10 - 0.79)	
No	658	339	326	174	332	165	0.58	(0.46 - 0.72)	

Table 16. OS Results by Other Subgroups

Baseline Risk Factor	Total n	# Deaths	PAC n	# Deaths	PAC/BEV n	# Deaths	Hazard Ratio	(95% CI)
All Patients	722	481	354	238	368	243	0.93	(0.78 - 1.11)
Region								
North America	663	443	324	219	339	224	0.92	(0.77 - 1.11)
Rest of the World	59	38	30	19	29	19	1.05	(1.56 - 1.99)
Disease Status								
Locally recurrent	12	6	4	3	8	3	0.00	(0.00 -)
Metastatic	709	475	349	235	360	240	0.95	(0.79 - 1.14)
Disease-Free Interval (mo)								
≤24	296	206	146	95	150	111	1.14	(0.87 - 1.51)
< 24	426	275	208	143	218	132	0.77	(0.61 - 0.98)
ER Status								
Positive	446	272	223	140	223	132	0.91	(0.72 - 1.16)
Negative	265	203	127	97	138	106	0.86	(0.65 - 1.13)
Unknown	11	6	4	1	7	5	3.96	(0.46 - 34.12)
ER/PR/HER2 combined								
Negative	232	180	110	84	122	96	0.89	(0.66 - 1.19)
All others	490	301	244	154	246	147	0.92	(0.73 - 1.15)
HER2 status								
Positive	15	8	6	2	9	6	3.54	(0.70 - 17.86)
Negative	650	433	316	211	334	222	0.94	(0.78 - 1.14)
Unknown	57	40	32	25	25	15	0.62	(0.32 - 1.18)
Measurable Disease at baseline								
Yes	472	323	243	166	229	157	0.99	(0.80 - 1.23)
No	250	158	111	72	139	86	0.85	(0.62 - 1.17)
Number of metastatic sites								
< 3	514	317	252	157	262	160	0.92	(0.73 - 1.14)
≥3	208	164	102	81	106	83	0.98	(0.72 - 1.34)
SLD of target lesions (mm)								
< Median	265	179	142	98	123	81	0.86	(0.64 - 1.15)
≥Median	262	186	132	94	130	92	0.99	(0.74 - 1.32)
Prior adjuvant hormone therapy								
Yes	343	232	175	118	168	114	0.95	(0.74 - 1.23)
No	379	249	179	120	200	129	0.91	(0.71 - 1.17)
Metastatic/Recurrence hormone therapy								
Yes	262	189	128	92	134	97	1.02	(0.77 - 1.36)
No	460	292	226	146	234	146	0.89	(0.71 - 1.12)
Prior adjuvant chemotherapy								
Yes	475	334	231	165	244	169	0.86	(0.69 - 1.06)

No	247	147	123	73	124	74	1.08	(0.78 - 1.49)
Prior taxane therapy								
Yes	142	102	68	53	74	49	0.67	(0.45 - 0.99)
No	580	379	286	185	294	194	1.00	(0.82 - 1.23)
Prior anthracycline therapy								
Yes	364	263	180	133	184	130	0.83	(0.65 - 1.05)
No	358	218	174	105	184	113	1.04	(0.80 - 1.36)
Bone only								
Yes	63	30	27	10	36	20	1.95	(0.88 - 4.30)
No	658	451	326	228	332	223	0.89	(0.74 - 1.07)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

1. In Study E2100, the sponsor's analyses had demonstrated a statistical significant result in PFS, but failed to show an advantage in OS. Also, FDA's confidence on the magnitude of the treatment effect (estimated 5.5 months' prolongation in median time to PFS) is affected by the following issues:

- a. The estimated treatment effect in PFS is sensitive to different assumptions on missing value and lost-to-follow-up

The primary analysis for PFS based on IRF assessment shows that the PAC/BEV arm had an estimated 5.5 month advantage over PAC arm in median duration of PFS. However, this 5.5 months advantage may not be reliable because Genentech was unable to collect scans for 10% of the study population and 247 (34%) of the patients were not followed until an IRF-determined PFS event or the end of study.

To assess the robustness of the magnitude of the PFS result in the presence of missing value and lost-to-follow-up, several sensitivity analyses were conducted by FDA with different assumptions for the outcome of missing value and lost-to-follow-up. The magnitude of the PFS result is sensitive to the different assumptions. The estimated difference in median duration of PFS varies from 0.4 to 4.1 months in these analyses (See Table 8 in Section 3.1.5. for detailed results).

- b. There is a substantial discordance between IRF radiologists and between IRF and ECOG radiologists in PFS determination

In order to assess the reliability of the radiologically-based, tumor-related endpoints, FDA evaluated the consistency between the two IRF radiologists, that working independently but reviewing the same information, in regarding the presence of disease progression and the data of progression. Among the 649 patients with scans available for IRF review, there were 217 patients, which account for 33% of the study population

where the two radiologists reached different conclusions regarding disease progression status or date of disease progression.

FDA also evaluated the discordance between IRF radiologists and ECOG radiologists in PFS determination. Across the entire study population, IRF and ECOG radiologists were not in agreement in 368 (51%) patients in either PFS status or PFS date.

FDA continues to gain experience regarding the reliability of radiologically-determined disease progression and at this time does not have sufficient experience to say whether the 33% rate of discordance between the IRF radiologists or the 51% rate of discordance between the IRF and ECOG radiologists are unusual. However, the level of discordance suggests a lack of reliability in the measurement of a given patient's PFS.

2. Study AVF2119g failed to indicate advantages in PFS (HR = 0.98) and OS (HR = 1.08) when adding bevacizumab to capecitabine (CAP) as a second line treatment of metastatic breast cancer.

5.2 Conclusions and Recommendations

This reviewer's evaluation of the Phase III Study E2100 supports the conclusion that bevacizumab, as first line treatment, delays time to progression or early death in patients with locally recurrent or metastatic breast cancer. However, Study E2100 failed to show an effect on overall survival (OS).

Additionally, the magnitude of the treatment effect on progression free survival (PFS) is not certain. Our confidence in the estimated 5.5 month improvement in median duration of PFS is limited by the following factors:

- Genentech was unable to obtain scans for 10% of patients.
- There are a large percentage of patients (34%) who were not followed until an independent review facility (IRF)-determined PFS event or until the end of study.
- The lack of reliability in determination of radiological disease progression and the date of progression between independent radiologists and between independent radiologists and study investigators.


Study AVF2119g failed to indicate advantages in PFS (HR = 0.98) and OS (HR = 1.08) when adding bevacizumab to capecitabine (CAP) as a second line treatment of metastatic breast cancer.

SIGNATURES/DISTRIBUTION LIST

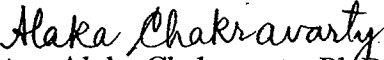
Primary Statistical Reviewer: Laura Lu, Ph.D

Date:  1/25/2008

Concurring Reviewer(s):

 1/25/2008

Statistical Team Leader: Mark Rothmann, Ph.D

 1/25/2008

Biometrics Division Director: Aloka Chakravarty, Ph.D

cc:

HFD-107/Ms. Sickafuse, Dr. Pai-Scherf, Dr. Gootenberg, Dr. Keegan

HFD-711/Dr. Lu, Dr. Rothmann, Dr. Chakravarty, Dr. Nevius, Ms. Patrician

HFD-711/Chron

7-24-07
Statistical Review and Evaluation

BLA: 125085-91 **Sn #:** 014

Supp Doc: Date Received: 5/15/2007

Biologics Name: avastin

Indication: metastatic breast cancer (MBC)

Statistical Reviewer: Laura Lu

Medical reviewer: Lee Pai-Scherf

Sponsor: Genentech Inc.

Meeting Schedule:

Background: This is a review for a supplemental statistical analysis plan under BLA 125085-91. BLA 125085-91 was originally submitted on 5/23/2006. The Agency considered the information and data submitted in the BLA inadequate for final approval action. On 9/8/2006, the Agency issued a complete response (CR) letter with a list of deficiencies to Genentech. Following further discussions with the Agency regarding the concerns in the CR letter, Genentech submitted a revised statistical analysis plan (SAP) for Study E2100 on 1/9/2007. Based on the Agency's comment on the revised SAP, Genentech submitted a further revised statistical analysis plan on 4/4/2007. This submission is a supplemental statistical analysis plan for the SAP submitted on 4/4/2007. Reference is made to the statistical review dated 7/24/2007 for SN#014.

Protocol Number and Title: Study ECOG E2100 is an ongoing, open-label, randomized, multicenter, controlled, phase III trial of paclitaxel versus paclitaxel plus avastin as first-line therapy for locally recurrent or metastatic breast cancer.

Summary of the Submission:

In this supplemental SAP, Genentech submitted additional analysis plans regarding missing data of progression free survival (PFS). Genentech defined two types of missing data:

- Completely missing radiographic images for the IRF assessment
- Missing timepoint response, defined as an UE (unable to evaluate) or ND (not done) timepoint response as defined in the E2100 IRF Procedure Document, Section 10.

For the two types of missing data, Genentech proposed the following analyses to describe the extend of missingness,:

1. Completely missing radiographic images will be summarized by treatment arm, including the number and percentage of patients with the following:
 - No radiographic data at baseline
 - No radiographic data at one or more post-baseline timepoints
2. Missing timepoint responses will be summarized by treatment arm, including the number and percentage of the patients with the following:
 - UE as the baseline assessment
 - UE as a timepoint response that is followed by disease progression

Additionally, Genentech proposed additional sensitivity analyses for PFS based the following rules in deciding PD date with missing value:

1. Every PD preceded by a UE assessment, irrespective of the oncologist's rationale for not backdating the PD, will be backdated to the UE immediately preceding the PD. This

serves as an extension to the primary method, in which the backdating of the PD date is dependent on the oncologist's review of individual patient data. PFS will be calculated based on the updated PD date.

2. For all patients, the PD dates will be based on the radiologist's read only, as this will have the effect of removing the clinical oncology data from the overall response assessment. Data for patients who develop missing PD dates because of this process will be censored in this analysis. PFS will be evaluated based on the updated PD dates.
3. All patients with missing PD dates resulting from the inability of the IRF to confirm progression will have their PD dates set as the date of the last tumor assessment +1 day. PFS will be calculated based on the updated PD dates.
4. The PD dates for patients in the paclitaxel + bevacizumab arm for whom PD could not be confirmed by the IRF will be set to the date of the last tumor assessment +1 day, whereas the PD dates for patients in the paclitaxel alone arm for whom PD could not be confirmed by the IRF will remain censored. PFS will be calculated based on the updated PD dates.

Statistical Issues and Comments to be conveyed to the Sponsor:

1. Please provide the number and percentage of patients missing at baseline and **each post-baseline visit** for 'completely missing radiographic images' and 'missing timepoint responses'.
2. In Section 5.2 of your submission, you stated that, in the primary analysis for PFS, 'When a timepoint assessment of PD is immediately preceded by a timepoint assessment of UE, the date of progression will be backdated by the oncologist reader for the overall read to the date of the previous UE assessment.' Please clarify whether PD event will be backdated if the radiographic images immediately preceding the event are completely missing.

Mark Rothmann 7/24/07

Concur: Dr. Rothmann

Cc:

HFD-107/Ms. Sickafuse, Dr. Pai-Scherf, Dr. Gootenberg, Dr. Keegan

HFD-711/Dr. Lu, Dr. Rothmann, Dr. Chakravarty

HFD-700/Ms. Patrician, Dr. Nevius

HFD-711/Chron



Laura Lu, Ph. D.

Mathematical Statistician

Date: ~~7/23/07~~

Statistical Review and Evaluation

BLA **125085-91** Sn #: 012

Supp Doc: Date Received: 4/4/2007

Biologics Name: avastin

Indication: metastatic breast cancer (MBC)

Statistical Reviewer: Laura Lu

Medical reviewer: Lee Pai-Scherf

Sponsor: Genentech Inc.

Meeting Schedule:

Background: This is a review for the amended statistical analysis plan under BLA 125085-91. BLA 125085-91 was originally submitted on 5/23/2006. The Agency considered the information and data submitted in the BLA inadequate for final approval action. On 9/8/2006, the Agency issued a complete review (CR) letter with a list of deficiencies to Genentech. Following further discussions with the Agency regarding the concerns in the CR letter, Genentech submitted a revised statistical analysis plan (SAP) for Study E2100 on 1/9/2007. This submission is a further revised statistical analysis plan based on the comments provided by the Agency for the previous revised SAP. Reference is made to Agency's letter dated 2/12/2007 to Genentech regarding the revised SAP on 1/9/2007.

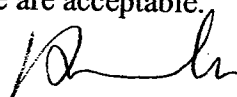
Protocol Number and Title: Study ECOG E2100 is an ongoing, open-label, randomized, multicenter, controlled, phase III trial of paclitaxel versus paclitaxel plus avastin as first-line therapy for locally recurrent or metastatic breast cancer.

Summary of Changes form the SAP submitted on 1/9/2007:

1. Genentech proposed to perform an analysis for overall survival based on the data with a cut-of date when the 481 event occurs, which constitute full information for survival. Genentech anticipated that full information will be available for inclusion in the clinical study report being prepared for the re-submission.
2. Genentech acknowledged that QOL analyses should be considered exploratory.

Statistical Issues and Comments to be conveyed to the Sponsor:

The changes made in this submission as summarized above are acceptable.



Laura Lu, Ph. D.

Mathematical Statistician

Date: **2/21/2007**

Concur: Dr. Rothmann

Cc:

HFD-107/Ms. Sickafuse, Dr. Pai-Scherf, Dr. Gootenberg, Dr. Keegan

HFD-711/Dr. Lu, Dr. Rothmann, Dr. Chakravarty

HFD-700/Ms. Patrician, Dr. Nevius

HFD-711/Chron



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number: 125085 / 91 12-22-06

Drug Name: Avastin

Indication(s): Metastatic breast cancer

Applicant: Genentech, Inc.

Date(s): Submitted 5/23/2006; PDUFA date 11/23/2006

Review Priority: Priority

Biometrics Division: Division of Biostatistics V (HFD-711)

Statistical Reviewer: Dr. Laura Lu, Ph.D,

Concurring Reviewers: Dr. Mark Rothmann, Ph.D, team leader
Dr. Aloka Chakravarty, Ph.D, Division Director

Medical Division: Division of Biological Oncology Products (HFD-107)

Clinical Team: Dr. Lee Pai-Scherf, MD, medical reviewer
Dr. Kaushikkumar Shastri, MD, team leader

Project Manager: Ms. Sharon Sickafuse

Keywords: Superiority, proportional hazard.

Background

This BLA was submitted on 5/23/2006. Study E2100 was the only Phase III clinical trial submitted in this BLA in supporting the efficacy of avastin, in combination with taxane-based chemotherapy, for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer. In Study E2100, 685 patients were randomized to two treatment arms (354 patients to the paclitaxel alone arm and 368 patients to the paclitaxel + bevacizumab arm). The median age of randomized patients was 55 years (range: 27–85 years). All patients were female except for 6 with no sex reported, and the majority of patients were White (76.2%). The primary endpoint of the trial was progression-free survival (PFS).

Data Sources

Datasets reviewed for this BLA were submitted electronically to the CBER electronic document room under Application #125085 . The datasets are in the CRT folder. The primary datasets reviewed are pate.xpt for efficacy results. All electronically submitted dataset for E2100 can be accessed at \\cbsap58\M\EDR Submissions\2006 BLA\DCC60002991\blamain\crt\datasets\e2100.

Review Conclusion

The data submitted in this BLA are inadequate for the reviewer to make a conclusion about the efficacy of the drug. The deficiencies regarding the data are:

1. The data submitted were not complete and cleaned. Not all patient follow-up information before 30 December 2005 (data transfer date) recorded in the investigator's report form were included in the submitted data. Not all patient data went through the cleaning process at the Eastern Cooperative Oncology Group (ECOG). ECOG is still collecting, entering and cleaning all study data, including patient information, safety and efficacy data, following the 30 December 2005 data transfer to Genentech.
2. Tumor data were not assessed by an independent review committee. So far, tumor data used by ECOG and Genentech consists solely of the investigator-reported tumor lesion measurements and comment fields.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Dr. Laura Lu, Ph.D

Date:

Concurring Reviewer(s): Dr. Mark Rothmann, Ph.D,
Statistical Team Leader

Aloka Chakravarty 12/22/06
OBV/OB Director: Dr. Aloka Chakravarty, Ph.D

cc:

HFD-107/Ms. Sickafuse
HFD-107/Dr. Pai-Scherf
HFD-107/ Dr. Shastri
HFD-107/Dr. Keegan
HFD-711/Dr. Lu
HFD-711/Dr. Rothmann
HFD-711/Dr. Chakravarty
HFD-700/Ms. Patrician
HFD-700/Dr. O'Neill

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125085 / S-091

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

****PRE-DECISIONAL AGENCY MEMO****

Date: February 13, 2008

To: Sharon Sickafuse, Project Manager
Division of Biologic Oncology Drug Products

From: Sean K. Bradley, Regulatory Review Officer *Sean K. Bradley*
Division of Drug Marketing, Advertising, and Communications

Subject: BLA 125085
Avastin (bevacizumab) For Intravenous Use
Proposed Product Labeling

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the proposed product labeling dated February 13, 2008 for Avastin and have the following comments. The proposed label was compared to the label of previously approved product Herceptin.

1. ADVERSE REACTIONS, Adverse Reactions in Clinical Trials, Metastatic Breast Cancer

The claim _____ minimizes the risks associated with Avastin. We suggest deletion of this claim.

b(4)

2. WARNINGS, PRECAUTIONS and ADVERSE REACTIONS

Will there be an update of the numbers included in these sections incorporating data taken from the breast cancer studies?

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Medical Officer's Consultation - Revised Independent Radiology Review

sBLA: [REDACTED].014 - Independent Radiology Review Revisions
Sponsor: Genentech, Inc.
ICL [IRF]: RadPharm
CRO: _____
Product: Bevacizumab (Avastin®)
Indication: Randomized Phase 3 Trial of Paclitaxel Versus Paclitaxel plus Bevacizumab (rhuMAb VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer
Requestor: Lee Pai-Scherf, MD, DBOP/OODP
Sharon Sickafuse, DBOP/OODP
Reviewer: Scheldon Kress, MD, DMIHP/OODP
Through: Dwaine Rieves, MD, Acting Director, DMIHP/OODP
Date: [REDACTED]

b(4)

S. Kress, MD

Attached is Genentech's response to FDA's letter of July 31, 2007 regarding the revised SAP and IRC charter they submitted on May 15th. In that letter DMIHP requested:

DMIHP's Request

1. Please clarify/revise the charter regarding the lack of provisions for qualification standards and training for quality assurance of the selected independent radiology readers. Will the independent radiology reviewers have a Training Manual?

DMIHP's Follow-up Response

Your submission states: "The Chief Medical Officer (CMO) reviews the test case performance of the new radiologist(s), and qualifies him or her according to RadPharm Standard Operating Procedures (SOPs)." It is not clear as to what criteria will be utilized to determine the necessity to re-train or replace the reviewers. Therefore, we recommend that you predefine an acceptable proficiency level for qualification to serve as readers for this trial.

Genentech's August 13, 2007 Response from RadPharm:

Re: Clarification to the E2100 Procedures Document

To Whom it May Concern:

The test cases used to qualify a new reader are cases that have been read by multiple radiologists. By virtue of multiple assessments a "gold standard" for the expected outcome has been established. The Chief Medical Officer compares the results generated by the new reader to the expected outcome (the "gold standard") and evaluates the proficiency of the new reader based on the lesions chosen for evaluation, the measurements of the lesions, the perception of new lesions, the reported Time Point Responses, Best Response, Date of First Response and Date of Progression if applicable. The Chief Medical Officer decides if the reported outcomes of the test cases are within the expected range based on prior assessments. If the reported outcomes are within the expected range, the reader is qualified. If the reported outcomes indicate the reader is medically proficient, but needs additional training related to the process of reviewing images for clinical trials, additional training is conducted and additional test cases are assigned, read and reviewed. If the radiologist's performance is not satisfactory, he/she is not employed as a reader.

FDA Response August 30, 2007

- 1 RadPharm's response provides adequate test case performance criteria to determine the proficiency level for the qualification of radiologists to serve as readers for the E2100 trial. The review methodology utilized by the Chief Medical Officer for reviews of the new radiologist(s) is acceptable.
2. However, the following question was not answered: "Will the independent radiology reviewers have a Training Manual?"

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Medical Officer's Consultation - Revised Independent Radiology Review

sBLA: [REDACTED] 014 - Independent Radiology Review Revisions
Sponsor: Genentech, Inc.
ICL [IRF]: RadPharm
CRO: _____
Product: Bevacizumab (Avastin®)
Indication: Randomized Phase 3 Trial of Paclitaxel Versus Paclitaxel plus Bevacizumab (rhuMAB VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer
Requestor: Sharon Sickafuse, DBOP/OODP
Reviewer: Scheldon Kress, MD, DMIHP/OODP
Through: Dwaine Rieves, MD, Acting Director, DMIHP/OODP
Date: July 26, 2007

b(4)

S. Kress, MD

[REDACTED] 7-26-07

1. Introduction

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

The document outlines the proposed statistical methods that will be applied to assess the impact of missing tumor assessment data on the analysis of progression-free survival (PFS), as assessed by an independent review facility (IRF) for Study E2100. This document supplements the methods described in Amendment 2 of the Statistical Analysis Plan (SAP; henceforth referred to as the primary SAP), which was submitted to Food and Drug Administration (FDA) on 4 April 2007. The purpose of this submission is to provide an update on an agreement to conduct an independent review of progression free survival results for study E2100 in support of a resubmission.

This Sponsor's submission makes reference to:

- Genentech's BLA supplement for the expansion of product labeling to include Avastin in combination with paclitaxel chemotherapy for first-line treatment of patients for locally recurrent or metastatic breast cancer (submitted on 23 May 2006)
- Complete Response letter for this application issued on 8 September 2006.
- Type A meeting held between Genentech and the Agency on 2 November 2006
- Correspondence from the Agency received 12 February 2007 regarding the E2100 IRF procedures document and handling of missing data in statistical analyses.

Specifically the Sponsor is submitting a revised IRF Charter, an analysis plan to address missing data, and a status update on their efforts to collect scans.

1. The IRF procedure document (IRF Charter) has been revised to include an independent review to validate the primary endpoint (PFS) on all subjects. Oncologist and radiologist training sections were expanded to reflect oncology and radiology reader qualifications, standards and training. In addition, changes to RadPharm personnel and responsibilities, changes in data management responsibilities to Genentech, Inc. are the major changes in this amendment.
2. The analysis plan for missing data supplements the methods described in the primary statistical analysis plan (amendment 12) which was submitted on 4 April 2007. The missing data analysis plan outlines the proposed statistical methods that will be applied to handle the missing data in statistical analyses of the primary endpoint, progression free survival as assessed by the Independent Review Facility (IRF). A retrospective review of radiographic images and pertinent medical records for the trial initiated more than 5 years after the activation of a trial will encounter a certain amount of missing data.
3. We provide a detailed account of the due diligence and status of our scan collection efforts. Scans were requested for a total of 578 patients (in addition to the 144 previously collected) at 232 sites including 3 countries outside of the U.S. to perform an Independent Radiology Facility (IRF) review. We have now collected scans for more than 90% of patients enrolled on study E2100. We intend to have the IRF include the interpretations of scans received by May 15, 2007 in the primary analysis.

2. Regulatory History

The first interim analysis for this study was conducted in April 2005. The ECOG Data Monitoring Committee (DMC) concluded that the primary endpoint of PFS had crossed the pre-specified O'Brien-Fleming boundary in favor of the paclitaxel + bevacizumab arm based on a data cutoff date of 9 February 2005.

The supplemental Biologics Licenses Application (sBLA) for Study E2100 was submitted on 23 May 2006.

On 19 July 2006, Genentech and the FDA held a teleconference to discuss the Agency's request for a complete independent and blinded review of all patients who experienced an objective response by investigator assessment to confirm response status and response duration. During the call, the FDA agreed to provide a reduced list of patients, which would be used by Genentech to conduct the audit.

On 21 July 2006, the FDA provided Genentech with a letter containing a list of 144 randomly selected patients (approximately 20% of the patients enrolled in Study E2100)

and requested that Genentech form an independent review committee to perform a complete, blinded review of all radiographic images and pertinent medical records to assess data integrity. The Agency requested that Genentech submit an IRF Procedure Document to the FDA for review prior to conducting the audit.

On 8 September 2006, the Agency issued a Complete Response Letter for the E2100 sBLA. The FDA delineated a number of issues in the response letter including the following, which highlight some of the missing data concerns:

1. The FDA noted that ECOG continued to collect, enter, and clean study data, including patient information and safety and efficacy data. For the submission, the FDA requested that all data be locked, completed, cleaned, and finalized. To this point, the FDA requested that Genentech submit a dataset that was clean as of a specified cutoff date based on the public dissemination of the initial interim data.
2. The FDA reiterated the need for an audit of the 144 patients specified in the 21 July 2006 letter and said further audits might be necessary.
3. The FDA requested a final and clean dataset for objective tumor response for all randomized patients, including those with measurable and non-measurable disease.
4. With regards to overall response rate and duration, the FDA requested that Genentech submit datasets that provide sufficient information to determine the cause of progression in patients with non-measurable disease and to confirm progression in those with clinical progression.
5. The FDA requested that Genentech provide a summary of missing data point assessments per timepoint, as specified in the primary SAP.

On 2 November 2006, Genentech met with the FDA to discuss Genentech's proposed responses to the Complete Response Letter and to obtain agreement on the proposed contents of the resubmission. Genentech proposed, and obtained agreement from the Agency, to provide an independent and blinded review of all 722 patients conducted by an IRF in order to verify the efficacy results. The IRF assessment will serve as the primary data source for the efficacy analyses. The FDA agreed with Genentech's proposal to submit an IRF Procedure Document for review using the Response Evaluation Criteria in Solid Tumors (RECIST), modified by incorporating current standard conventions for applying the originally published criteria.

In addition, Genentech agreed to implement a cutoff date of 9 February 2005 for all efficacy analyses contained in the resubmission sBLA. This would allow the Agency to review data that most closely reflected what might have been available to the ECOG DMC when they concluded that the primary endpoint of PFS had crossed the pre-specified O'Brien-Fleming boundary in favor of the paclitaxel + bevacizumab arm.

Genentech re-submitted a Supplemental Statistical Analysis Plan for Protocol E2100 in the treatment of breast cancer: "Randomized Phase 3 Trial of Paclitaxel Versus Paclitaxel plus Bevacizumab (rhMAB VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer" on May 14, 2007 [BL 125085/91.014]. DMIHP responded to the sponsor's request on January 23, 2007. In the current submission for Protocol E2100 documentation is provided for revisions to address the FDA's comments/concerns. Specifically, the briefing document provided formal responses (both explanations and revisions) to the SAP as relates to the IRC and concerns of the DMIHP.

3. Consultant's Recommendations

We have completed our review of the relevant materials provided for adequacy of the charter/document to comply with the FDA's request for charter revision, clarification, modification (provided in the DMIHP Review document dated January 23, 2007).

The following section provides the Sponsor's explanations and proposed revisions to the IRC and SAP as they relate to the concerns of the DMIHP and the DMIHP's follow-up response (*detailed in Italics*):

DMIHP's Request

1. Please clarify/revise the charter regarding the lack of provisions for qualification standards and training for quality assurance of the selected independent radiology readers. Will the independent radiology reviewers have a Training Manual?

Sponsor's Reply

The Chief Medical Officer (CMO) reviews the test case performance of the new radiologist(s), and qualifies him or her according to RadPharm Standard Operating Procedures (SOPs). Once qualified, radiologists may be assigned to read protocols on a sub-specialty basis. Work is monitored on a daily basis according to the Quality Plan that has been written for, distributed to, reviewed with, and Approved by the Division of Medical Imaging and Hematology Products.

DMIHP's Follow-up Response

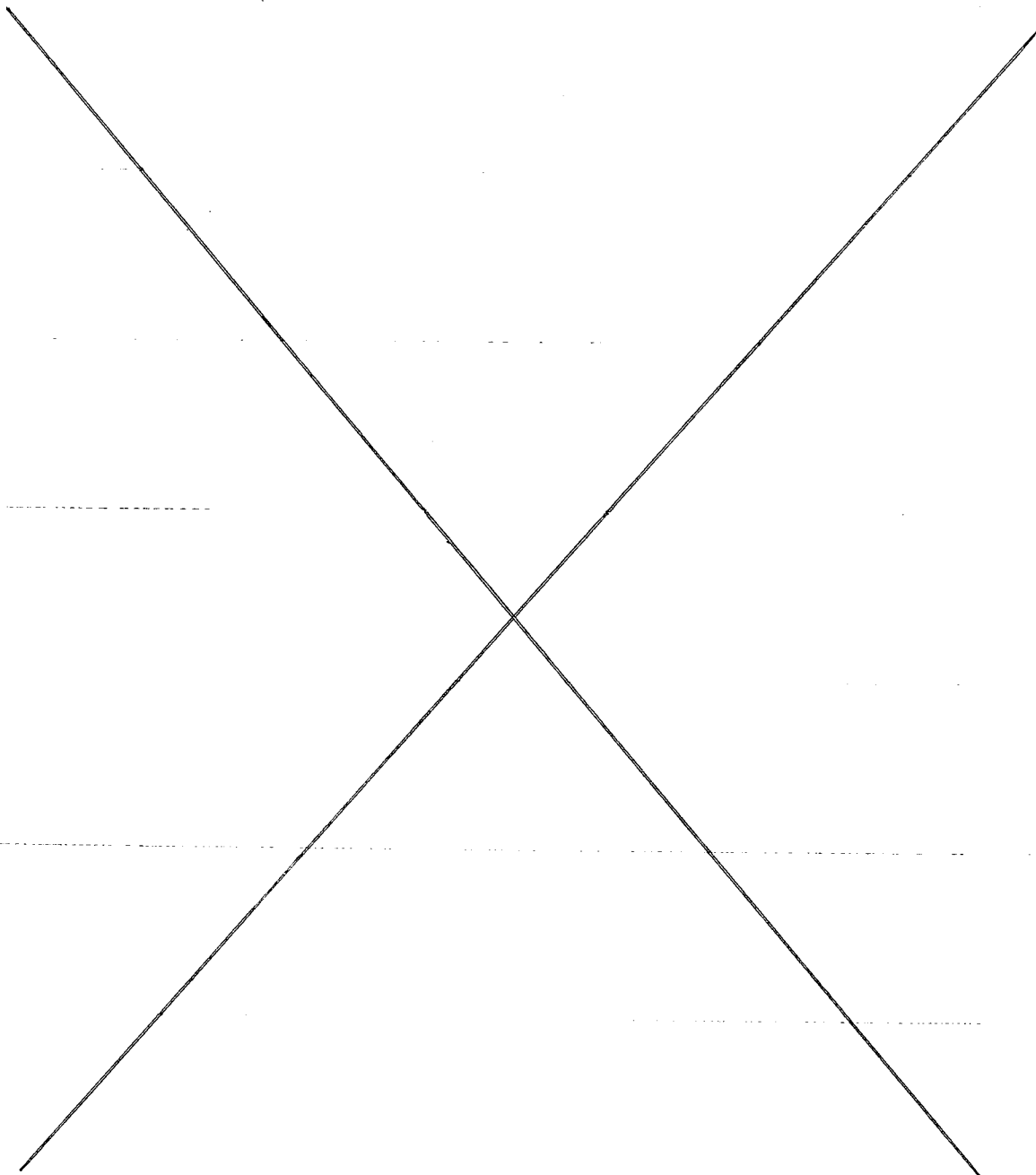
The submission states: "The Chief Medical Officer (CMO) reviews the test case performance of the new radiologist(s), and qualifies him or her according to RadPharm Standard Operating Procedures (SOPs)." It is not clear as to what criteria will be utilized to determine the necessity to re-train or replace the reviewers. Therefore, we recommend that you predefine an acceptable proficiency level for qualification to serve as readers for this trial.

DMIHP's Request

2. Whereas missing data are to be expected, please pre-specify the provisions for handling of all potential missing data as related to missing time points, data validation, technically inadequate quality images, proposed modifications, and justifications.

Sponsor's Reply (Quoted directly from the Sponsor's submission)

b(4)



4 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

DMIHP's Follow-up Response

The DMIHP agrees that the Sponsor's proposed changes (explanations and revisions) to the SAP have adequately addressed the division's concerns for the handling of missing data in this trial. This document adequately addresses the factors that contributed to missing data, the types of data that are expected to be missing, conservative review assessments, and proposed sensitivity analyses for the evaluation of the anticipated types of missing data.

4. Study Design

Study E2100 was an open-label, randomized, multi-center, controlled, Phase 3 trial conducted predominantly in the United States by the Eastern Cooperative Oncology Group (ECOG) in collaboration with seven other cooperative groups and the clinical trial support unit (CTSU). In addition, 12 U.S. patients were enrolled through the expanded participation program (EPP), and 59 patients were enrolled from study sites in South Africa (37) and Peru (22) through collaborations with ECOG. A small number of other international patients from North America were enrolled by NCI Canada (NCIC).

This study evaluated paclitaxel + bevacizumab versus paclitaxel alone in patients with locally recurrent or metastatic breast cancer who had not previously received chemotherapy for metastatic disease. The study was activated in 2001; by 26 May 2004, enrollment was complete, with 722 patients randomized. To minimize potential bias that might arise from an open-label study, the primary objective of this study was changed to PFS based on a retrospective, blinded, independent review of radiologic and pertinent medical data by an IRF. This objective was agreed upon between the FDA and Genentech on 2 November 2006.

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Medical Officer's Consultation – Independent Radiology Review

sBLA: ~~125085/91~~ - Independent Radiology Review
Sponsor: Genentech, Inc.
CRO: RadPharm
Product: Bevacizumab (Avastin®)
Indication: Randomized Phase 3 Trial of Paclitaxel Versus Paclitaxel plus
Bevacizumab (rhuMAB VEGF) as First-Line Therapy for Locally
Recurrent or Metastatic Breast Cancer
Requestor: Sharon Sickafuse, DBOP/OODP
Reviewer: Scheldon Kress, MD, DMIHP/OODP
Through: George Mills MD, Director, DMIHP/OODP
Date: January 23, 2007

S. Kress MD
OK for Mills
12902

1. Background

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

Genentech Inc. submitted a supplemental Biologics License Application (sBLA) to support the use of Avastin® in combination with taxane-based chemotherapy for the treatment of patients who had not received chemotherapy for their locally recurrent or metastatic breast cancer. This sBLA was submitted on May 23, 2006. Review by the Division of Biologic Oncology Products determined on September 8, 2006 that the information and data submitted for Protocol E2100 to support the sBLA were inadequate for final approval action at that time, primarily due to the non-blinded nature of the study and the lack of pre-specified, detailed and objective (blinded and independent) radiological and clinical parameters for determination of disease progression.

During the sBLA review, it was noted that tumor data used by Genentech to determine the key efficacy endpoints of PFS and response rate, consisted solely of subjective investigator-reported tumor lesion measurements and comment fields rather than independent reads.

In support of regulatory approval for the proposed new indication, Genentech has submitted a sBLA based on a re-read of the data from Protocol E2100 (sponsored by NCI and ECOG). Genentech will perform due diligence to collect scans on all 722 patients. This consult is limited to evaluation of the adequacy of the charter/document to confirm

the primary endpoint of PFS and the modified RECIST criteria for this post hoc review. The re-read process is described in the procedures document provided by RadPharm to satisfy the requirements for performing an Independent Radiology Review. RadPharm will be responsible for evaluation and tabulating the clinical Time Point Responses; Genentech will then be responsible for analyzing the data and determination of the primary endpoints of PFS.

The final procedures document has been amended at Genentech's request to revise the sections on Confirmed Response and Oncology Assessments. For response confirmation, if more than one assessment time point is missing, then confirmation is not recommended. This change makes the review more conservative and in-line with standard practices. In addition, changes to oncology assessments were made whereby assessment processes and data handling were standardized by having all subjects undergo an oncology review.

2. Consultant's Recommendations

We have completed our review of the relevant materials provided for adequacy of the charter/document to confirm the primary endpoint of PFS and the modified RECIST criteria for this post hoc review.

We have the following comments for the DBOP to consider regarding the adequacy of the Independent Review Charter and RESIST criteria to assess all relevant pertinent information to confirm the primary endpoint. However, these responses are proposals only and should be modified, consistent with precedent as well as regulatory and clinical perspectives.

Even though these issues may not be subject to remedy, they will impact on the reliability of the study results, and therefore we have concerns regarding the following factors:

1. The lack of standardization, the lack of pre-specified uniformity in the methods of collection of radiological and clinical data at prespecified timepoints, and the lack of uniform availability of data for all subjects to all Radiological and Oncological reviewers.
2. The difficulty in performing a retrospective (post-hoc) review of images performed without prespecified imaging requirements or protocol. Assessment of objective time point response comparison measurements utilizing the modified RECIST criteria is potentially further confounded by:
 - Changes in imaging modalities or technical parameters of scans.
 - Use or lack of use of oral contrast agents for each imaging study.
 - Use or lack of use of intravenous contrast agents for each imaging study.
 - Lack of uniformity in image acquisition due to variations in individual radiology facility's imaging protocols.

3. Utilization of the radiologist assessment as the final assessment for subjects without medical information pertinent to an oncology review (when the oncologist confirms the absence of medical information).

In addition, we propose the following request for charter revision, clarification, modification, listed here in the sponsor-ready format:

4. Please clarify/revise the charter regarding the lack of provisions for qualification standards and training for quality assurance of the selected independent radiology readers. Will the independent radiology reviewers have a Training Manual?
5. Whereas missing data are to be expected, please pre-specify the provisions for handling of all potential missing data as related to missing time points, data validation, technically inadequate quality images, proposed modifications, and justifications.

Assessment of the acceptability of the modifications to the Confirmed Response proposed by Genentech and RadPharm as provided in Table 3 could be evaluated best by the clinical team in DBOP.

3. Introduction – Protocol E2100

Title of Protocol:

A Randomized Phase 3 Trial of Paclitaxel versus Paclitaxel plus Bevacizumab (rhuMAB VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

This is a phase 3, open-label, randomized, multicenter study. Eligible subjects were randomized in a 1: 1 ratio to therapy consisting of either: Arm A: Paclitaxel + Bevacizumab or Arm B: Paclitaxel. Each cycle was repeated every 4 weeks until disease progression or unacceptable toxicity.

Primary Objective:

To evaluate the efficacy of bevacizumab plus paclitaxel compared with paclitaxel in patients with chemotherapy-naïve metastatic breast cancer, as measured by progression-free survival.

Secondary Objectives:

To compare the objective response rate, duration of response, and overall survival of paclitaxel to that of the combination of paclitaxel plus bevacizumab.

Objective of Independent Review:

Independent Review Committee (IRC) - The objective of the Independent Review Committee (IRC) in this retrospective review is to assess tumor response and progression for selected subjects enrolled in the Protocol E2100.

4. Image Acquisition and Management

Genentech will identify to RadPharm a selected group of subjects from Protocol E2100 that will require independent review. All available imaging studies that were performed on these subjects including the assessment dates recorded in the database will be collected by the investigators in E2100 and sent to RadPharm by courier. ECOG will provide the site contact information. RadPharm will handle the logistics of image retrieval. RadPharm will receive the scans and will notify the sites and Genentech of missing exams/information. Genentech acknowledges that contractual arrangements for scan retrieval are between Genentech and ECOG. ECOG is responsible for enforcing compliance of the sites with respect to these issues, as RadPharm has no contractual arrangement with the sites.

Because this is a retrospective review of radiographic images, prospective site qualification will not be performed.

Images may be sent to RadPharm as CDs, ODs or hard copy images. When the site sends scans as CDs or ODs, a mutually agreeable digital interchange format will be established that provides the highest quality digitization processes. If for any reason, RadPharm equipment cannot read the digital media, the site is notified. The radiology department is contacted to see if another digital interchange format can be agreed upon. If not, the site is instructed to send second original films that will be digitized by RadPharm. Multiple time points may be included on one disc, however for identification purposes, only one subject per disc is required. ODs and/or CDs should be labeled on the outside with an identification sticker. RadPharm keeps the discs sent with images as source documentation. Sites must maintain their own copies of digital data for the retention period applicable to the protocol, Good Clinical Practice (GCP), and federal and state legal and medical requirements. Paper study reports will not be accepted.

Image Quality Assessment (IQA) Process

The RadPharm project team member identifies the exam dates and/or time point(s) to undergo Image Quality Assessment/Copy Quality Assessment (IQA/CQA) and completes an IQA/CQA Request Form.

Each image is:

- Assessed for quality, consistency and appropriateness according to established radiological standards.

- Checked to verify the exam date and subject identification.
- Baseline exam dates for study E2100 are verified with the randomization date.
- Checked to identify the exam type (CT, MRI, etc) and the body area being examined - Chest, Abdomen, Pelvis, etc.
- Recorded as a separate entry in the tracking database.
- Verified that the imaging requirements for each time points are satisfied: each exam is complete, images are not missing, windows are not missing, etc.

There can be no images that were acquired or reconstructed which were not filmed. The exception is sagittal or coronal CT reconstructions, If these were done at the site, they do not need to be sent to RadPharm for review. Each image is assessed for the presence of any grease markings, computerized measurements and/or annotations that may bias the radiologist or obscure independent measurement of lesions.

The image quality and readability are assessed. The quality of images is recorded in the tracking database, The quality of any image duplication/copy is assessed as compared to the originals. Quality and readability are assessed according to the following criteria:

- The image border does not obscure any image data/anatomy,
- A reference measurement scale, appropriate and representative of the field of view (FOV) and magnification factor used for scanning, is present on each image. The measurement scale on the film must be in centimeters. Hard copy films that will be digitized and read digitally must have a measurement scale for calibration.

The reason(s) the images failed IQA and the action(s) to resolve the IQA issue(s) is/are recorded in the tracking database. Contact with the sites to resolve IQA issues is initiated and described in a Contact Sheet. Any IQA issues will be noted and will always remain in the project-specific spreadsheet with the IQA date and resolution entered in the appropriate cell.

Digital images that pass IQA are committed to the Digital Image Management System (DIMS), placed in subject folders and prepared for radiologist review. Hard copy films that pass IQA are digitized, committed to the DIMS, blinded, and prepared for radiologist review.

IRC Image Reading Process

Images for the IRC radiology review will be read according to a "Sequential Locked Read" paradigm. The purpose of this approach is to evaluate the drug under study in the same manner as the investigator who will evaluate the subject clinically, This process is applied when a succession of time points are available to be read for a particular subject. In order to keep the radiologists completely blinded and unbiased, a work list is prepared for each radiologist, specifying the following instructions for each time point:

- The baseline shall be read, and then locked.
- The first time point (after baseline) shall be read with access to the baseline for "Review Only", and then locked. "Review Only" indicates that no changes to the baseline measurements or annotations shall be possible for that radiologist.
- The second time point shall be read with access to the baseline and first time point for review only, and then locked.
- As each time point is read, the radiologist or recording assistant shall transcribe his/her measurements onto the source document and make his/her response assessment and sign that document before proceeding to the next task in the work list (reading the next time point),
- Each successive time point shall follow the paradigm outlined above.
- Once a time point has been locked, a flag is set in the annotation file that prevents any subsequent changes for that user. This step is permanent and cannot be subsequently overridden under work list control.
- Under no circumstances may a radiologist (or any other user) change his/her own measurements or annotations or any other radiologists' measurements or annotations once they have been locked,
- If a clerical error (as opposed to a change in interpretation) is detected that requires correction, whether it is identified by the radiologist him/herself or during a subsequent Quality Control (QC) process:
 - No changes shall be made to the image annotations and measurements (such as modification of the size of a lesion, removing a lesion, adding a new lesion), either by the radiologist (since they are locked), or other staff (since all annotations and measurements are specific to the user who made them and cannot be changed by another user),
 - The radiologist or a technologist as guided by the DIQC process may re-label an incorrectly labeled annotation (e.g. if annotations of lesions, which are by default sequentially numbered, are not numbered according to convention, e.g. for lesion "0" to be correctly renumbered to "001", etc.).
 - In the instance where errors are identified, GCP-compliant corrections shall be made to the source document.
 - If, in hindsight, a radiologist would have changed his/her response assessment of a time point while reviewing a subsequent time point (as opposed to correcting a clerical error changed), the response assessment will be recorded on the source document for the subsequent time point in the comments section,
 - No change shall be made to the original time point on the source document.
 - In terms of response assessment, the different interpretation shall be propagated forward to the subsequent time point and to any following time point, including the determination of Best Response,

This process is intended to provide for the sequential locked read methodology to be rigorously enforced, allowing for the correction of purely clerical errors on the source documents, to allow image, measurement and response assessment data sets to be submitted that are correct and internally consistent, and to allow use cases to be invoked.

To avoid the introduction of "unscheduled" assessments after a read on a succession of time points has been completed, a confirmation will be required from the respective sites stating that all available time points have been received by RadPharm prior to the read. RadPharm will inform Genentech of any expected scans that are unobtainable during the collection process. In addition, RadPharm will perform a cross check with the scans and dates sent from the Genentech database to ensure there are no missing scans prior to the read.

Tumor assessments will be identified by cycle/time point based upon subject enrollment. During a reading session, the radiologist will not know how many time points are being presented to him/her for review for that particular subject.

Table 1 Imaging Requirements - Tumor Assessment Schedule Protocol E2100

Exam	Pre-Study (Within 4 weeks before randomization)	Every 3 Cycles	Off- Treatment Follow-Up¹
Tumor Assessment	R	R	R

R: Required. "Scans or X-Rays" were required to document measurable and non-measurable disease.

¹ Follow-up after subject discontinues protocol therapy, every 3 months if subject is < 2 years from study entry; every 6 months if subject is 2-5 years from study entry,

5. Independent Radiology Reviewer Training

Each radiologist assigned to read study E2100 will independently review the Procedures Document, Source Document and Instructions for Completion of the Source Document specific for this study. The PM or designee will conduct a full review of the above documents with all radiologists assigned to this study and will also discuss issues specific to this study. Procedures Document training for each radiologist will be documented and signed by the PM or designee and radiologist. Radiologists will sign financial disclosure

forms at the time of training. These financial disclosure forms will be available for review by regulatory authorities when required.

Noted was the lack of provisions for qualification standards and training for quality assurance of the selected independent radiology readers and for a Training Manual.

6. Independent Central Blinded Radiologic Read

Study Efficacy Evaluation

Each selected subject will have an efficacy evaluation that includes a review of all the submitted imaging studies performed while on trial. No clinical information will be supplied to the radiology reviewers as part of this retrospective review. All images will be reviewed and response assessed using the modified RECIST criteria provided.

RadPharm will assign subjects to radiologists and the radiologists will read tumor assessments for the selected subjects in this trial. The radiologists read all images for each subject without knowing the response assessment from the site or ECOG reviews. Independently, two different radiologists will read all time points for each trial subject. The reads will be designated "Radiology Read Number 1" and "Radiology Read Number 2". Neither radiologist (1 nor 2) will have access to the other radiologist's measurements or assessments. Each radiologist will complete standard RadPharm source documents for his or her independent reads. Every source document will undergo 100% Quality Control (Qc).

The PM or designee will complete the appropriate section of a "Read Comparison Source Document" page that will compare the results of Radiology Read Number 1 and Number 2. The variables for each subject to be entered on the "Radiology Read 1 and 2 Comparison Source Document" page and thus to be compared are:

- the Overall (radiographic) Response,
- the Date of Progression (if applicable),
- the Date of First Response

The PM or designee will compare the results entered on the "Read Comparison Source Document" page. If the data as listed above are identical, there will be no adjudication required between Read Number 1 and 2. The PM or designee will sign the appropriate section of the "Read Comparison Source Document", verifying no adjudication is required. If any of the information is "discordant," Radiologist Number 3 will perform an adjudication of the radiology results, as described below. If there is no discordance, the results from Radiologist 1 will be used for determination of Overall Response, Date of Progression, and Date of First Response.

Adjudication of Radiology Results

The adjudicating radiologist (Radiologist Number 3 which cannot be either of the two primary radiologists, Radiologist 1 or 2) will review the "Radiology Read Number 1 Source Document" and "Radiology Read Number 2 Source Document" which have been transcribed by a project team member, and signed by the reading radiologists. In addition, the adjudicator will also review the image and annotation files of Radiologists 1 and 2.

The adjudicator must not know the identity of the two primary radiologists. For this reason the adjudicator will review exact copies of the Source Documents. However the signatures of the reading Radiologists Number 1 and Number 2 will be blinded.

For Level 1 adjudication, the adjudicator will review, but not re-read, the two (2) prior reads. The adjudicator may make measurements to verify previously made measurements. Any electronic measurements made by the adjudicator will be saved on the images as annotation files.

The adjudicator will choose the read that he or she believes most accurately represents the Overall Response, Date of Progression, and Date of First Response, The read chosen by the adjudicator will be used to determine the Overall Response, Date of Progression, and Date of First Response.

For Level 2 adjudication (the adjudicator may not agree with either radiologist on the Overall Response, Date of Progression, or Date of First Response). In this situation the adjudicator will re-read the case and provide the Overall Response, Date of Progression, or Date of First Response, as required. The reading process for the adjudicator will be as previously described for a primary read. This read will then be used to determine the Overall Response, Date of Progression, and Date of First Response.

Integrity of the Reading Process

Response assessments performed by RadPharm will be an independent function and not subject to input from Genentech or ECOG, its designees, or any site involved in this clinical trial. In an effort to avoid the introduction of bias to the reading sessions, the data received by the reading radiologists at RadPharm will be limited to data that is relevant to an independent assessment of tumor response and disease progression. The reading radiologists will not have access to outside radiology reports or investigator classification of response.

Additional Clinical Information

At the time of the radiology review, no additional clinical information other than the imaging studies will be provided.

In addition to the above, the oncologist will receive clinical information from the ECOG database. This information is limited to cytology results, tumor measurements assessed

by clinical examination, and comments collected on disease evaluation forms, non-target lesion supplemental forms, and long-term follow-up forms. These comments will be reviewed by the RadPharm project team who will redact any information that could potentially bias or unblind the oncologist.

Data Handling during Radiology Reviews

Digital images, either those primarily acquired from OD, CD or those scanned from film, which have passed IQA and been blinded, are presented to the reader for interpretation. The reader logs onto the workstation system using an identifier code and unique password; the radiologist may not provide/transmit this password to any other individual. Once logged into the system, the radiologist logs into the read application using an identifier code and unique password. Once logged into the application, the radiologist is presented with a "work list" which lists subjects and time points available to be interpreted. The "work list" constrains the radiologist to review only those images to which he/she has been given access,

When a "work list" task is selected, the images and any previous measurements (by the same radiologist) for the baseline and/or the appropriate successive time points are retrieved from the repository. These are then available to be displayed for longitudinal comparison. Once measurements are saved/committed, the measurements cannot be changed by any "work list" user,

The validated software application allows the window center and width of the displayed images to be adjusted, linear distance measurements of target lesions to be made, and non-target lesions to be outlined. The radiologist reviews the baseline scans and identifies all sites of disease present at baseline. The sites of disease are classified as target or non-target lesions as described. Subsequent time points are reviewed in chronological sequence according to the sequential locked read methodology previously described.

All measurements of lesions as well as annotations and calibrations are made by the radiologist who was logged into the application and are attributable to the radiologist who made them. All measurements, calibrations and annotations are then checked back into the repository along with the images, for inclusion of this information in the audit trail.

RadPharm radiologists will assess response and the radiologists or a data-recording assistant will record all data on the source document. The radiologists and the recording assistant will sign and date the source document.

The source document will be filed in a study-specific binder, and a copy filed in the off-site (archival) study binder. Once completed, the original source document will undergo routine QC and QA.

Data from the IRC review will be sent to Genentech electronically as discussed below in the Data Management Section.

7. Radiographic Characterization of Disease Sites

Imaging Assessment

The radiologists will independently evaluate imaging studies obtained as per the E2100 protocol. The protocol indicates the same examinations should be used to assess identified lesions at all time points, however detailed technical radiographic specifications were not prospectively identified as part of this protocol. Therefore, there may be instances where the same examinations were used to evaluate lesions at subsequent time points; however the technical specifications of how the exams were performed might be different. In this instance, the radiologists will comment during the read as to whether or not the technical differences in the exams affect the response evaluation.

Ultrasound should not be used for assessment of visceral lesions, but can be used to assess superficial lesions such as skin lesions or lymph nodes or masses during on-study efficacy evaluation. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules or to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Lesions identified on chest x-ray (CXR) are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however CT is preferable.

Response Criteria

As noted above, all images will be reviewed and tumor response assessed according to modified RECIST. At baseline, tumors are categorized as Measurable or Non-Measurable according to the following definitions:

Definitions of Measurable

Using modified RECIST criteria, measurable lesions are defined as uni-dimensionally measurable disease greater than or equal to 20 mm in the longest dimension as determined on the baseline scan with conventional CT scan or lesions that can be accurately measured in at least one (1) dimension with the longest diameter (LD) being two (2) times the reconstruction interval (RI) of the spiral CT scan if spiral CT is used. Depending on the RI of the spiral CT the measurable lesion size may be ≥ 10 -16 mm. For example, a spiral CT scan done at 8 mm RI would have a minimum lesion size of 16 mm in the longest dimension. The minimum size of a measurable lesion is 10 mm.

Definitions of Non-Measurable

Using Modified RECIST criteria, all other lesions, including small lesions that measure less than 20 mm in the longest dimension with conventional or less than 10 mm with spiral CT, and other truly non-measurable lesions, are considered non-measurable.

Baseline Images

Baseline images will be used to prospectively identify all sites of disease present at the start of treatment. Sites of disease will be characterized as either target or non-target lesions. Up to ten (10) target lesions (a maximum of five (5) per organ) will be chosen to measure over the course of therapy. All other sites not chosen as target lesions are characterized as non-target lesions. This will include any measurable lesions that were not chosen as target lesions. Target lesions should not be chosen from an area that is suspected on the basis of the imaging studies to have received radiation therapy. Although the specific information about radiation therapy fields, dose and progression of disease in the prior radiation fields was not prospectively captured, the radiologists will use their medical judgment to determine if a lesion exists in a previously irradiated field.

Target Lesions

Target lesions will generally be the largest lesions, most reliably measured, and most representative of the subject's sites of disease, and must be measurable at baseline. For any target lesion at any time point, measurements will be taken and recorded unidimensionally. The longest dimension (LD) of each target lesion will be measured and recorded. The LD of the target lesions will be summed to obtain the Sum of the Longest Diameters (SLD). The baseline SLD will be used as reference to further characterize the objective tumor response of the target lesions.

For the consideration of progressive disease (PD), the nadir of the SLD for the target lesions will be used as reference. Target lesions will be measured at each time point. For cases where there are no target lesions identified, tumor assessment should be done based on non-target lesion assessments. In this scenario, PR is not an option. Assessment will be based upon modified RECIST criteria.

Lytic bone lesions assessed by cross-sectional imaging techniques (CT/MRI) with a soft tissue component can be selected as target lesions.

Non- Target Lesions

All of the sites of disease present at baseline not classified as target lesions will be Classified as non-target lesions. Non-target lesions will be qualitatively assessed at each subsequent time point. Examples of non-target lesions include:

- Lytic bone lesions without a soft tissue component
- Leptomeningeal disease
- Irradiated lesions
- Inflammatory breast disease and non-measurable skin lesions
- Measurable lesions beyond the maximum number of ten (10)
- Groups of lesions that are small and numerous
- Pleural effusion/pericardial effusion/ascites
 - Significant effusions (for example a pleural effusion that opacifies one half of the hemithorax), ascites and other fluid collections that are present at baseline should be considered malignant
 - An unequivocally significant increase in pleural effusions, ascites or other fluid collections in a stable or responding subject indicates PD.
 - New, unequivocally significant fluid collections in a stable or responding subject indicates PD
 - In a stable or responding patient recurring effusions and other fluid collections are only considered PD if significant (for example a pleural effusion that opacifies one half of the hemithorax),

New Lesions

New lesions are those that were not present at baseline or at the prior time point. At each time point, the presence of new lesions will be determined. All new lesions, that are not too small to measure (i.e., at least 5 mm in LD) and are not thought to be benign by the reviewer, will be considered malignant and result in the determination of PD. New lesions seen on a bone scan in a stable or responding subject should unequivocally represent PD before this is assigned. This determination is generally made on the basis of the number and distribution of the lesions as well as correlation with other imaging modalities to exclude the possibility that new areas of abnormal uptake are related to benign causes and/or the flare phenomena.

Lesions that are encountered (subsequent to the baseline) in anatomic locations that were not scanned at baseline are considered PD. Measurable lesions that were present, which subsequently resolved and then recurred will be considered new lesions and will represent unequivocal PD, Non-target lesions that were present, which subsequently resolved and then recurred will not be considered PD unless the findings are unequivocal for progression of malignancy.

8. Radiologic Image Review

Radiologist Assignment

It is RadPharm's intent that the same two (2) radiologists will be assigned to review all images for a subject during this trial. If a radiologist leaves RadPharm during the course of the trial, or becomes disabled for a period of more than 30 days, Genentech will be informed of the change and a new radiologist with similar experience, qualifications and training as the original member will be assigned and will continue with that subject until the trial is concluded. The response assessments provided by both the prior and the new radiologist will be used to determine response. Specifically the new radiologist will begin reading the unread time points, based on the target lesions identified by the prior radiologist.

Lesion Measurements

All measurements will be determined using electronic calipers, measured and reported in millimeters (mm), and recorded uni-dimensionally. The LD will be recorded on the source document. The SLD for all target lesions will be calculated and reported as the baseline SLD. Lesions that resolve will be recorded as having measurements of 0 mm.

For each specific target lesion, the site code will be identified and the accompanying standard descriptor will be used. For example, a mass in the right lung will have site code R29 followed by the description "lung mass." The alphanumeric site code plus the alpha description will be included for each target lesion on the source document. Target lesions will be numbered from 001 to 010.

For non-target lesions, multiple lesions may be grouped together and assessed as a group. For example, there may be external iliac, internal iliac and common iliac nodes. As target lesions these would be individually identified. As non-target lesions they are grouped together as 83, which is the site code for non-target lesion pelvic adenopathy. The alphanumeric site code plus the alpha description will be included for each non-target lesion on the source document. Non-target lesions will be numbered from 200 to 299,

New lesions will be numbered from 300 to 399.

If one tumor engulfs (merges) with another tumor, the new tumor will be measured in its LD, and will now be measured as a single independent lesion. This new lesion will be recorded in the same category as it was at baseline (target or non-target), with comments recorded by the reading radiologist at that time point, then recorded as follows:

Sample of Radiologist Reading and Measurement

	Lesion #	Description	Measurement (mm)
At Baseline	2	Lung	20
	3	Lung	10
At End of Cycle X	2	Lung (merged with 3)	30
	3	Lung (merged with 2)	NA

Reporting Conventions

Unable to Evaluate (UE) Lesions Category

This category is reserved for lesions (target and non-target) that were imaged but for some reason could not be measured or evaluated (i.e., due to poor radiographic technique or poorly defined margins). Examples would be a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe, or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples the boundaries of the lesion would become difficult to distinguish. Every effort will be made to assign measurements to lesions that develop less distinct margins because they become much smaller. Lesions that cannot be measured or evaluated will be classified for that time point as Unable to Evaluate (UE). Once a target site of disease is classified as UE, the SLD cannot be determined and will not be recorded unless the SLD of the assessed lesions confirm progression. A response of CR, PR or SD cannot be assigned for that time point.

If one or more non-target site(s) of disease have been classified as UE, and all the target lesions have been evaluated, a response of PR or SD can be assessed. CR cannot be assessed as all sites of disease cannot be proven to have resolved, PD can also be assessed in this instance if the rules for progression apply.

Note: If a lesion is classified as UE at Time Point X, and is adequately evaluated at the next Time Point (X+1), the response will be determined for the Time Point X+ 1. If the response at Time Point X+ 1 is PD, the Date of Progression will be recorded as the date of the prior UE time point.

Not Done (ND) Lesions Category

Target and non-target lesions that were identified at baseline, which were not evaluated at a subsequent time point because 1) scans were not completed at this particular time point or not available for RadPharm review, or 2) the lesion in question was not included on the scan at this particular time point, will be classified as Not Done (ND). If a target lesion is classified as ND for a particular

time point, the SLD cannot accurately be determined for that time point. A response of CR, PR, and SD cannot be assessed for that time point.

If one or more non-target site(s) of disease have been classified as ND, and all the target lesions have been evaluated, a response of PR or SD can be assessed, CR cannot be assessed as all sites of disease cannot be proven to have resolved. PD can also be assessed in this instance if the rules for progression apply,

Note: If a lesion is classified as ND at Time Point X, and is adequately evaluated at the next Time Point (X+1), the response will be determined for the Time Point X+1. If the response at Time Point X + 1 is PD, the Date of Progression will be recorded as the date of the prior ND time point.

Too Small to Measure (TSTM) Lesions Category

Target lesions that are being followed and, after baseline, decrease in size to less than 5 mm will be categorized as Too Small To Measure (TSTM). A lesion will be assigned a value of 5 mm for the purpose of the calculation of the SLD. If a lesion subsequently increases in size to greater than or equal to 5 mm in one dimension, its true size will be recorded. The purpose of the assigned value for the measurement is the acknowledgment that small lesions are not accurately measured.

9. Evaluation of Radiographic Response Per Timepoint

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the SLD of target lesions taking as reference the baseline SLD.

Stable Disease (SD): Neither sufficient shrinkage of target lesions to qualify for PR or sufficient increase to qualify for PD taking as reference the nadir SLD since the treatment started.

Progressive Disease (PD): At least a 20% increase in the SLD of target lesions taking as reference the smallest sum of the longest diameters recorded since the treatment started or the presence of one or more new lesions. In addition, when target lesions become TSTM (too small to measure), PD will not be determined for a time point unless there has been both a 20% increase in the SLD and an actual increase in SLD of at least 10 mm.

Unable to Evaluate (UE): A target lesion present at baseline which was not measured or which was unable to be evaluated (UE) leading to an inability to determine the status of that particular tumor for the time point in question (procedure described above).

Not Applicable (NA): No target lesions were identified at baseline.

Not Done (ND): Scans were not performed at this time point to evaluate the target lesions or scans were not available for RadPharm review.

Evaluation of Non-Target Lesions

Each non-target lesion will be qualitatively evaluated at each time point. Response of each non-target lesion at each time point is assessed with respect to the baseline status. Progression of each non-target lesion(s) is assessed with respect to nadir size of the non-target lesion(s). The overall non-target lesion response for each time point will be assessed as the worst case for the non-target lesion(s) for that time point. Response assessments are defined as follows:

Complete Response (CR): Disappearance of all non-target lesions.

Stable Disease (SD): The persistence of one or more non-target lesions not qualifying for CR or PD,

Progressive Disease (PD): The "unequivocal progression" of existing non-target lesion(s) or appearance of one or more new lesion(s) is considered progressive disease (PD). If PD for the subject is to be assessed for a time point based solely on the progression of non-target lesion(s), then additional criteria are required to be fulfilled. In this instance, the lesion(s) upon which the assessment of PD is being made must be retrospectively assessed from baseline (or the nadir) and compared to the time point in question. The radiologist will retrospectively review the nadir scan, and measure the size of the non-target lesion(s). The radiologist will record these measurements in the comments section of the source document for the time point where progression has occurred. PD of non-target lesion(s) in this instance will be assessed when the SLD of the lesion(s) has increased by 20% or greater and any new unequivocally malignant lesion(s) are identified that measure at least 5 mm in LD. If the non-target lesion(s) do not meet the quantitative criteria as described, they will not be assessed as having progressed.

Unable to Evaluate (UE): A non-target lesion present at baseline which was not measured or was unable to be evaluated (UE) leading to an inability to determine the status of that particular tumor for the time point in question.

Not Applicable (NA): No non-target lesions were identified at baseline.

Not Done (ND): Scans were not performed at this time point to evaluate the non-target lesions or scans were not available for RadPharm review.

Response Determination

Time Point Response (TPR)

Response at each time point will be assessed as a combination of the target and non-target responses as well as the presence of new lesions. This is termed the Time Point Response (TPR). TPR is assessed with reference to baseline for the determination of response and the nadir tumor size/nadir SLD for evaluation of PD. The TPR for each time point will be determined as described above, even if the prior time point demonstrates PD. TPR is assessed according to the following hierarchy:

Target lesions will be assessed by applying the definitions described above and the target lesion response will be recorded separately on the source document.

Each non-target lesion will be assessed separately and an overall response of the non-target lesions will be categorized and recorded on the source document. The worst response of any non-target lesion is used to categorize the overall response of the non-target lesions,

The presence or absence of new lesions will be assessed and recorded as Yes/No. The location and size of new lesions will be recorded. A new lesion must be at least 5 mm to be assessed as such unless a fluid collection or a bone lesion on a bone scan,

Time Point Response (TPR) Table

TPR will be determined at each time point according to **Table 2** and recorded separately on the source document. TPR will be determined according to the following criteria using all available evaluations. All target lesions identified at baseline must be evaluated at each pre-determined imaging time point otherwise CR, PR, or SD cannot be assessed.

Table 2 : Time Point Response (TPR) Table

TIME POINT RESPONSE*

Target Lesions	Non-Target Lesions	New Lesions	Time Point Response
CR	CR	No	CR
CR	SD	No	PR
CR	UE/ND	No	PR ¹
PR	UE/ND	No	PR ¹
PR	Non-PD/NA**	No	PR
SD	UE/ND	No	SD ¹
SD	Non-PD/NA**	No	SD
PD	ANY	Yes/No	PD
ANY	PD	Yes/No	PD
ANY	ANY	Yes	PD
UE	Non-PD/NA**	No	UE
ND	Non-PD/NA**	No	UE
NA*	SD	No	SD
NA*	CR	No	CR
NA*	NA**	No	UE

*: The 1st Time Point Response, other than PD and SD, can only be made after the subject is On-Study for a minimum of 7 weeks (49 days) from date of randomization. If the subject is not On-Study within this minimal time period, any tumor assessment before 7 weeks (49 days) from date of randomization will have a time point response of UE (unable to evaluate). A time point response of SD can only be made if the subject has been assessed at a minimum interval of 8 weeks from the randomization date. Assessments satisfying the criteria for SD but occurring prior to 8 weeks from the randomization date will have a time point response of UE (unable to evaluate).

NA*: No target lesions identified at baseline.

NA**: No non-target lesions identified at baseline.

¹: At any time point, if a non-target lesion is classified as UE/ND, a time point designation of PR/SD (not CR) may be assigned based on information from the target lesions. However, the response will only be considered to be confirmed if all sites of disease present at baseline are evaluated at the time of the confirmatory radiological assessments or at a subsequent assessment and the results are consistent with response.

Confirmed Response

RadPharm will determine if a response is confirmed, by applying the TPR from an initial and subsequent assessment as per Table 3. This table is obtained from a modified proposal from the RECIST working group in assessing two (2) sequential time point response assessments. Subsequent shall mean sequential in all but two cases:

- (1) an initial CR followed by a single TPR of UE or ND, and
- (2) initial PR followed by a single TPR of UE, ND, or SD,

In these cases, confirmation shall be based on the next TPR following the UE/ND/SD.

For example, a PR followed by single time point response of SD, UE or ND followed by a subsequent PR allows confirmation of the first PR. Scans are required to confirm a CR or a PR no earlier than four (4) weeks (28 days) from the time a response of CR or PR is

first suspected, SD does not require confirmation, Subjects must have been on trial and have had a radiologic assessment after baseline at least 8 weeks (56 days) (2 cycles) from date of randomization before they can meet the criteria for SD. Unconfirmed PR and CR will be downgraded to SD.

Table 3 : Confirmed Response Based on An Initial and Subsequent Assessment

1st Time Point Response**	Subsequent Time Point Response	Confirmed Response
PD	No further evaluation	PD
UE/ND	PD	PD
CR	PD	PD or SD (1)
PR	PD	PD or SD (1)
SD	PD	PD or SD (1)
CR	CR	CR
CR	UE/ND***	UE/ND or SD (1)
PR	CR	PR
PR	PR	PR
PR	SD*** (2)	SD (2)
PR	UE/ND***	UE/ND or SD (1)
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	UE/ND	UE/ND or SD (1)
UE/ND	CR	SD
UE/ND	PR	SD
UE/ND	SD	SD
UE/ND	UE/ND	UE/ND

*The purpose of this table is to illustrate that unconfirmed objective responses (PR or CR) will be downgraded/classified as stable disease. Confirmation of response must be ≥ 4 weeks from the assessment at which PR (CR) was determined.

** The 1st Time Point Response, other than PD and SD, can only be made after the subject is On-Study for a minimum of 7 weeks (49 days). If the subject is not On-Study within this minimal time period, any tumor assessment before 7 weeks (49 days) will have a time point response of UE (unable to evaluate).

***A CR can be confirmed by a subsequent documented CR if there is a single intervening time point with a response of UE/ND. A PR can be confirmed by a subsequent documented PR if there is a single intervening time point with a response of UE/ND or SD. If the subsequent Time Point Response confirms the CR (or PR) then the Confirmed Response will be CR (or PR). If the subsequent Time Point Response after UE is PD, then the Date of Progression will be the date of the UE exam [example PR UE PR = PR, PR UE PD = PD at Date of UE].

- (1) Subjects are required to be on trial at least 8 weeks (56 days) from date of randomization before an assessment of SD can be made. Assessments satisfying the criteria for SD but occurring prior to 8 weeks from the randomization date will have a time point response of UE (unable to evaluate). SD does not require confirmation.
- (2) Response is SD if the increase from the 1st to the 2nd assessment does not qualify for PD.

10. Best Response (at each Tumor Assessment/Time Point)

At each time point the best response the subject has achieved until that particular time point will be assessed by reviewing all time points up to and including that tumor assessment or time point. A best response of CR or PR cannot be assessed unless it is confirmed. The best response, other than PD or SD, can only be made after the subject is on study and has had a tumor assessment at least 7 weeks (49 days) from date of randomization. If the subject is not on study within this minimal time period, any tumor assessment before 7 weeks (49 days) from date of randomization will have a best response of UE (unable to evaluate).

Overall Response

This will be recorded as the best confirmed response the subject has had while on the trial. This will be recorded separately on the source document. The overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since treatment started), The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Response Assessment Exceptions

Cases with incomplete anatomical coverage by CT at baseline

Cases with incomplete anatomical coverage by spiral CT scan at baseline will be allowed as long as there is full anatomical coverage at the subsequent time point and there is no evidence of disease in the applicable area the first time this anatomical region is scanned.

Cases where there are no target lesions identified by RadPharm

In cases where RadPharm cannot identify target lesions at baseline, the response will be assessed on the basis of the non-target lesions. In this scenario, PR is not an option.

Cases where lesions are seen in an anatomic site that was not scanned at baseline

In cases which lesions are seen at a subsequent time point in an area that was not scanned at baseline, the rules for progression will apply,

Assessment Date Conventions

It is acknowledged that an assessment may include several methods of evaluation performed over a period of several days within a window of time around an expected assessment date. The convention to be followed when assessing response will be to assign a single date to evaluations performed over more than one day, but less than ± 7 days and to record the date of response (CR, PR, SD) as the date of the last radiographic evaluation included in the series for that assessment (e.g. if a patient had a CT on 01 Mar which demonstrated PR and an MRI on 03 Mar which demonstrated PR, the date of PR would be recorded as 03 Mar). For progression (PD) the recorded date is the date that

progression was first demonstrated (e.g., if the patient had a CT Chest on 01 Jan and CT abdomen 03 Jan and progression was seen only in the abdomen, then the date of PD is 03 Jan. If progression was seen on both scans then the date chosen is always the earlier scan date thus 01 Jan).

11. Independent Blinded Oncology Review Process

Oncologist Training

Each oncologist assigned to read study E2100 will independently review the Procedures Document, source documents, and instructions for completion of the source document specific for this study. The PM or designee will conduct a full review of the above documents with all oncologists assigned to this study and will also discuss issues specific to this study. Procedures Document training for each oncologist will be documented and signed by the PM or designee and oncologist. Oncologists will sign financial disclosure forms at the time of training if required. These financial disclosure forms will be available for review by regulatory authorities when required,

Oncologist Assessment

All subjects will have an oncology review completed by an oncologist at RadPharm. The oncology review will be part of the on-study efficacy evaluation. The information for the oncology review will come from the ECOG database as described and will be supplied to RadPharm by Genentech or ECOG. For subjects without medical information pertinent to an oncology review, the oncologist review will consist of confirming the absence of medical information, and the radiologist assessment becomes the final assessment.

Baseline

At baseline the oncologist will prospectively identify all sites of non-radiographic clinical disease present at the start of treatment. All clinical sites of disease will be considered non-target lesions, as the independent oncologist cannot make independent measurements of lesions seen on physical exam by the investigator.

Non-Target Lesions

Non-target lesions will be qualitatively assessed at each succeeding time point. Examples of non-target lesions include: Lesions measured by the investigator, not independently confirmed by the RadPharm reviewer, Groups of lesions that are small and numerous,

The oncology non-target lesions are listed on the Oncology Review source document, with the lesion numbering consecutive, beginning with the radiology non-target lesions, For example, if the reading radiologist identifies five (5) radiographic, non-target lesions, the lesions would be listed or identified as non-target lesions, numbers 200-204 (according to the numbering convention) on the Radiology source document. If there were an additional three (3) clinical lesions to the radiographic lesions, these lesions would be listed on the Oncology Review source document as non-target lesions numbers

205, 206 and 207. The response assessed on the Oncology Review source document would represent the oncology non-target lesions. The response assessed on the Overall Response page by the oncologist would be a combination of both radiology and oncology assessments. In all cases, radiology evaluation should take precedence where a lesion is assessed both radiographically and by physical exam,

For example, if axillary adenopathy is seen on CT of the chest, and by physical exam, the assessment should be made on the CT exam. During the oncology review, the reviewer should comment on the fact that the assessments were made based on the images, and therefore, were not clinically evaluated by the oncologist.

New Lesions

New lesions are those that were not present at baseline or the prior time point. At each time point, the presence of new lesions will be determined. All new lesions, irrespective of their size, not thought to be benign by the reviewer, will be considered malignant and result in the determination of PD. Measurable lesions that were present, which subsequently resolved and then recurred, will be considered new lesions and will represent unequivocal PD. Non-target lesions that were present, which subsequently resolved and then recurred will not be considered PD unless the findings are unequivocal for progression of malignancy.

Oncology Response Assessment

The oncologist will review the assessments performed by the radiologist and will identify non-target lesions according to the definitions provided. The oncologist has the ability to review the image files on subjects where it is required for response assessment. For oncology response assessment and overall response assessment, the reader will follow the established definitions.

The oncologist will determine TPR (radiology and oncology), best response at each time point, and the best overall response for the subject while on the trial. The oncologist will also determine the date of progression, according to the guidelines for dates for response and progression provided.

Data Handling During Medical Reviews

The oncologist will complete RadPharm Oncology Source Documents and assess an oncology response on the basis of the clinical information. The oncologist at the completion of a reading session will sign the source documents for that subject. At each time point, the oncologist will list those clinical findings relative to the time point based on the information provided. The source documents will be titled "Oncology Source Document" and "Overall Response Source Document." The original paper source documents will be filed in a study binder, behind subject-specific tabs, and a copy filed in the off-site study binder. Once completed, if corrections are necessary to the original RadPharm paper source documents for the purposes of data clarification or correction,

they will be made according to GCP as required following internal QC, QA and query resolution, before completion on the paper source documents.

Any changes made to the source documents will have an audit trail of the changes maintained in paper format on the original source document. The changes will be made by the original reading oncologist or another reading oncologist on the trial and the corrected data, the reason for the change, the date of the change and the initials of the oncologist will be recorded.

12. Data Management

Response assessments performed by RadPharm will be an independent function and not subject to input from Genentech or ECOG, its designee or investigative site of the clinical trial. Radiologists or recording assistants will enter data at the time of the read on standard RadPharm source document. The radiologists will sign the source document.

Signature of the source document is considered a "locked dataset." Digital Image Quality Control (DIQc) comparing 100% of the entries on the source document to the image files will be performed as described below. A QA check as per the QA plan developed for this protocol will also be performed on the source document. Subsequent to the radiology review, data from the signed source document will be data entered using industry standard double data entry procedures. The data will be transferred via a mutually agreed-upon electronic format. Any queries to the dataset based on listings review performed by Genentech will be returned to RadPharm via an EXCEL issues spreadsheet. The RadPharm Project Manager (PM) will screen queries returned to RadPharm for data resolution. All queries involving medical decisions of image interpretation will be referred to the reading radiologist for resolution and signature. In special circumstances, such as when the reading radiologist is not available, the RadPharm CMO or his designee has the ability to answer these queries.

The queries will be resolved by the RadPharm project team and will include the change, the reason for the change, the person who made the change, and the date the change was made. The EXCEL issues spreadsheet will be used to maintain an audit trail for any changes to the "locked data set." An established audit trail will be available from a review of the signed source documents, and the EXCEL issues spreadsheet. RadPharm will transfer another dataset to Genentech should any changes to the locked dataset be required as a result of data query resolution.

APPLICATION NUMBER:
BLA 125085 / S-091

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: STN 125085/91 Supplement Type (e.g. SE5): _____ Supplement Number: N/A

FDA Received Date: 5-24-06 Action Date: 2-23-08

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 and rectum (in combination with intravenous 5-fluorouracil-based chemotherapy).

First-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children

- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:

Sharon Sickafuse

Regulatory Project Manager

cc: NDA/BLA #
 HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03; revised 8-10-04 for RMS/BLA use)

Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Monday, February 25, 2008 1:50 PM
To: Sickafuse, Sharon
Subject: FW: reason for censoring in patients with non-measurable disease

From: Pai-Scherf, Lee
Sent: Friday, February 08, 2008 4:59 PM
To: 'Lisa Bell'
Subject: FW: reason for censoring in patients with non-measurable disease

Lisa,

Please:

1. Confirm the information presented in the following table: Reasons for censoring for patients with non-measurable disease.
2. Provide the reason for the difference for the number of patients with non-measurable disease by IRF versus ECOG.

Please provide me Genentech's response by Tuesday, Feb 12.

Thanks.

Lee

Reasons for censoring for patients with non-measurable disease.

TRT	reason	COUNT	percent among censored
PAC	total	52	100.00%
	censor		
PAC	no scan	22	42.31%
PAC	NPT	12	23.08%
PAC	by IRF not by ECOG	8	15.38%
PAC	other	10	19.23%
PAC/BEV	total	89	100.00%
	censor		
PAC/BEV	no scan	22	24.72%
PAC/BEV	NPT	23	25.84%
PAC/BEV	by IRF not by ECOG	11	12.36%
PAC/BEV	other	33	37.08%
total	total	141	100.00%
	censor		
total	no scan	44	31.21%
total	NPT	35	24.82%
total	by IRF not by ECOG	19	13.48%
total	other	43	30.50%

LICENSING ACTION RECOMMENDATION

Applicant: Genentech, Incorporated

STN: 125085/91

Product:

Bevacizumab

Indication / manufacturer's change:

In combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast 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 2-21-08 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: Lee Pai-Schiff Date: Feb 21, 2008

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: 2-19-08
- Cleared from Hold Date: _____

Compliance status check Not Required

Regulatory Project Manager (RPM) Sharon Sickafuse Date: 2-22-08

Responsible Division Director R Pazum Date: 2/22/08
(where product is submitted, e.g., application division or DMPQ)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Center for Drugs Evaluation & Research - Food & Drug Administration

Chana Fuchs, Ph.D.
Division of Monoclonal Antibodies
NIH Campus, Building 29B, Room 3NN06, HFD-123
Telephone (301) 827-0712
Facsimile (301) 827-0852

Date: February 20, 2008

From: Chana Fuchs, Ph.D.

To: BLA 125085/91 File

A handwritten signature in black ink, appearing to be "Chana Fuchs", is written over the "From:" line.

Product: Bevacizumab (Avastin)

Dosage form/strength/use: liquid single use vials of 100mg and 400mg for IV infusion

Sponsor: Genentech Inc.

License Number: 1048

Subject: BLA 125085/91: Categorical Exclusion for Environmental Assessment

This efficacy supplement is for use of Avastin in combination with taxane based chemotherapy as first-line therapy for treatment of locally recurrent or metastatic breast cancer.

The sponsor has submitted a request for EA categorical exclusion under 21 CFR 25.15(d) and 21 CFR 25.31(c). There is no information in this supplement indicating that any additional environmental information is warranted.

The claim of categorical exemption is accepted.

Genentech

IN BUSINESS FOR LIFE

DEPARTMENT OF REGULATORY AFFAIRS

1 DNA Way MS#241B
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

February 20, 2008

Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **License No. 1048**
STN: BL 125085/91
AVASTIN[®] (bevacizumab)
Request for Review under CFR 601.40, Subpart E

Dear Dr. Keegan:

We refer to Genentech's Biologics License Application (BLA) for AVASTIN[®] (bevacizumab) in combination with intravenous 5-fluorouracil-based chemotherapy for the first line treatment of patients with metastatic carcinoma of the colon or rectum, approved on 26 February 2004. Reference is also made to Genentech's BLA supplement for the expansion of product labeling to include AVASTIN[®] in combination with paclitaxel chemotherapy for first-line treatment of patients for locally recurrent or metastatic breast cancer (resubmitted on 23 August 2007).

The purpose of this submission is to request the Agency's review of this supplement (BL125085/91) under the regulations pertaining to 21 CFR 601.40, Subpart E -- Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

In accordance with 21 CFR 601.41, and the requirement for the further study of Avastin in patients with metastatic breast cancer, Genentech commits to execute and provide results from an unprecedented number of trials for the purposes of providing evidence of clinical benefit in this setting. Satisfactory review of the results of:

1. BO17708 (AVADO) "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study To Evaluate The Efficacy and Safety of Bevacizumab in Combination With Docetaxel in Comparison With Docetaxel Plus Placebo, as First-Line Treatment for Patients With HER2-Negative Metastatic Breast Cancer". The protocol was submitted to BB-IND 7023 on January 8, 2008 (Serial No. 1179). The study was completed (database lock) on February 4, 2008.
2. AVF3694g "A Multicenter, Phase III, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer". The protocol was submitted to BB-IND 7023 on August 14, 2007 (Serial No. 1025). The study will be completed on February 28, 2009.

will be required for the conversion of this accelerated approval. Specifically, we commit to submit an efficacy supplement encompassing final study reports, summary analyses, primary datasets and revised labeling for both trials by July 1, 2009.

Additionally, we commit to:

1. AVF3693g "A Phase III, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Treated Metastatic Breast Cancer". The protocol was submitted to BB-IND 7023 on January 9, 2007 (Serial No. 838). Completing patient accrual by June 30, 2009. Completing the study by March 31, 2010. A final study report, summary analyses and primary datasets will be submitted by January 31, 2011.
2. CALGB 40503, "Endocrine Therapy in Combination with Anti-VEGF Therapy: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Endocrine Therapy Alone or Endocrine Therapy plus Bevacizumab for Women with Hormone Receptor-Positive Advanced Breast Cancer". The protocol was submitted to BB-IND 7023 on January 19, 2007 (Serial No. 845). Completing patient accrual by February 29, 2012. Completing the study by September 30, 2012. A final study report, summary analyses and primary datasets will be submitted by December 31, 2013.
3. BO20231 "A Randomized, Open-Label, 2-Arm, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Trastuzumab/Docetaxel Compared with Trastuzumab/Docetaxel Alone as First Line Treatment for Patients with HER2 Positive Locally Recurrent or Metastatic Cancer". The protocol was submitted to BB-IND 7023 on February 20, 2007 (Serial No. 872). Completing patient accrual by July 31, 2011. Completing the study by April 30, 2012. A final study report, summary analyses and primary datasets will be submitted by April 1, 2013.

Patricia Keegan, M.D.
February 20, 2008
Page 3

If you have any questions regarding this submission, please contact Lisa M. Bell, Ph.D.,
Director, Regulatory Affairs at (650) 225-3512.

Sincerely,

Todd W. Rich, M.D.
Vice President
Development Regulatory Affairs, Medical Communication, Drug Safety and Quality

Sickafuse, Sharon

From: Kiel, Hea S
Sent: Tuesday, February 19, 2008 3:33 PM
To: Sickafuse, Sharon
Cc: CDER-TB-EER
Subject: FW: request for compliance check fro STN 125085/91

Sharon,

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the Therapeutic Biologic-EER request below. There are no pending or ongoing compliance actions to prevent approval of STN 125085 / 91 at this time. The status is as follows:

Manufacturer	FEI Number	Inspection Date	Classification	Profile
Genentech, Inc South San Francisco CA	2917293	4/9 ~ 27/07	NAI	SVS:AC
Genentech Inc. Vacaville, CA	3002902534 CFN2954595	9/22 ~ 29/06	VAI	CBI :AC
Genentech, Espana Porrino (Pontevedre) Spain	3003134808	9/14 ~ 22/06	VAI	CBI

HeaSuk Kiel
Consumer Safety Officer
FDA/CDER/OC/DMPQ/HFD-323
Phone: 301-796-3246
Fax: 301-827-9069

From: Sickafuse, Sharon
Sent: Monday, February 11, 2008 11:08 AM
To: CDER-TB-EER
Subject: request for compliance check fro STN 125085/91

Sponsor: Genentech, Inc.

STN: 125085/91

New Indication: Treatment of metastatic breast cancer

Action due date: Friday, February 22, 2008. I apologize for the extremely short notice! Until Friday, this supplement was going to receive a complete response letter.

Drug Substance Facilities:

Genentech, Inc.
DNA Way
South San Francisco, CA 94080
2917293/SAN

Genentech, Vacaville
1000 New Horizons Way
Vacaville, CA 95688
954595

Genentech, Espana
Aptdo. De Correos #85
La Relba, s/n
36410 Porrino (Pontevedre)
Spain
3003134808

Drug product, final vial labeling, and distribution occur at the San South Francisco facility.

Contact person: Mary Sliwkowski, Ph.D., Senior Vice President, Regulatory Affairs, Quality, and Compliance
650-225-1202

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

MEMORANDUM

To: STN 125085/91

From: Sharon Sickafuse, RPM *SKS*
Division of Biologic Oncology Products
Office of Oncology Drug Products

Date: February 14, 2008

Subject: teleconference with Genentech

The clinical team (Drs. Pai-Scherf, Keegan, and Pazdur) and I contacted Genentech to request that in addition to results from study BO17708, that data from studies AVF3694g, AVF3693g, CALGB 40503, and BO20231 also be submitted as post marketing commitments. Studies BO17708 and AVF3694g will be the confirmatory studies to convert accelerated approval to regular approval.

Genentech agreed to FDA's request and will submit a letter.

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Thursday, February 14, 2008 3:54 PM
To: 'Lisa Bell'
Subject: Bev PI

Attachments: BEV PI FDA revisions_FEB14 .doc

Here you go.

Please send me the final draft PI.



BEV PI FDA
revisions_FEB14 .do.

44 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: Wednesday, February 13, 2008 4:42 PM
To: 'Lisa Bell'
Subject: Bev PI & PMCs

Attachments: BEV PI FDA revisions_FEB13.doc

Hi Lisa,

Here's the PI.



BEV PI FDA
revisions_FEB13.doc.

Also, regarding PMCs,

In addition to the AVADO trial, the team would like to talk about the other studies listed on Appendix A of the document that GNE presented at the January 7th meeting.

I have 2-4pm tomorrow blocked off for any labeling/PMC discussions.

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Tuesday, February 12, 2008 4:36 PM
To: 'Lisa Bell'
Subject: Bevacizumab PI

Attachments: BEV PI FDA revisions_FEB12.doc

Here you go:



BEV PI FDA
revisions_FEB12.doc.

Disclaimer: This label does not yet reflect input from all management levels.

47 Page(s) Withheld

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

 √ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Sickafuse, Sharon

From: Sickafuse, Sharon
ent: Monday, February 11, 2008 11:08 AM
o: CDER-TB-EER
Subject: request for compliance check fro STN 125085/91

Sponsor: Genentech, Inc.

STN: 125085/91

New Indication: Treatment of metastatic breast cancer

Action due date: Friday, February 22, 2008. I apologize for the extremely short notice! Until Friday, this supplement was going to receive a complete response letter.

Drug Substance Facilities:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
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3003134808

Drug product, final vial labeling, and distribution occur at the San South Francisco facility.

Contact person: Mary Sliwkowski, Ph.D., Senior Vice President, Regulatory Affairs, Quality, and Compliance
650-225-1202

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

Memorandum

Date: February 8, 2008
From: *Karen D. Jones, Chief, Project Management Staff* ^{KDJ}
CDER/OND/OODP/DBOP
Subject: Genentech Avastin sBLA 125085/91

FDA Participant: Karen D. Jones, CPMS

Genentech Participant: Lisa Bell, Ph.D., Director, Regulatory Affairs

After initially leaving a voice message, I was able to speak with Lisa Bell of Genentech regarding sBLA 125081/91 (Avastin for treatment of breast cancer) to inform her that FDA is requesting that Genentech submit a request for accelerated approval for this application. Dr. Bell indicated that she was expecting the contact as a follow-up to a telecon between Dr. Pazdur and Genentech management. I requested that Genentech submit the following information by Monday morning, February 11, 2008:

- A request for accelerated approval under 21 CFR Subpart E.
- A proposed PMC with all milestones for the confirmatory study, the AVADO study.
- Revised labeling in standard labeling format. I noted that the application was originally submitted in May 2006, and thus is not subject to implementation of the labeling in PLR format at this time, as per the conditions set out in 21 CFR 201.56.
- A commitment to turn around all FDA proposed labeling revisions within 18 hours of receipt in order to reach agreements in the available time.

Dr. Bell questioned whether the AVADO study would be considered the confirmatory study given that the primary endpoint was PFS. I confirmed that FDA will consider the AVADO study the confirmatory study; our expectation is that Genentech will submit both PFS data and OS survival data obtained from the study.

The call concluded.

Addendum: Later this same date, Lisa Bell contacted FDA to ask if it will be acceptable to submit the revised labeling in red-line tracked changes with line numbers, but not annotated, given the short amount of time to meet FDA's requested time frame. I agreed that FDA would accept a red-line MS WORD version of the labeling in the initial submission along with a memo containing the annotation comments. Genentech agreed and stated that submission of an annotated version would follow as soon as possible.

The call concluded.

Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Wednesday, January 16, 2008 11:32 AM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon; Lu, Hong (Laura)
Subject: STN 125085/91: Information Request - subgroup analyses for OS

Lisa,

For the E2100 study, please provide subgroup analyses of overall survival by the factors shown in the following table:

Baseline Risk Factor	Total n	#Events	PAC n	#Events	PAC/BE n	#Events	Hazard ratio	(95% CI)
Region								
North America								
Rest of the World								
Disease Status								
Locally recurrent								
Metastatic								
Measurable Disease at baseline								
Yes								
No								

I would appreciate if you can send me the results by Tuesday, Jan 22.

Thanks.

se

Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Wednesday, 12/16/2009 9:37 AM
To: 'Lisa Bell'
Cc: Lu, Hong (Laura); Sickafuse, Sharon
Subject: [REDACTED] Information request

Dear Lisa,

I hope you had a nice holiday break.

We have the following information request regarding E2100:

At the ODAC meeting on Dec 5th, Genentech presented a table indicating that 37% of the patients were lost to follow-up. Please provide the table with break down of reasons for loss to follow-up as well as the SAS program(s) to support the findings.

Thanks.

Lee

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
ODDP/CDER/FDA
WO22, Rm 2314
Ph 301-796-1430

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Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Monday, December 10, 2007 1:23 PM
To: 'Lisa Bell'
Cc: Lu, Hong (Laura); Sickafuse, Sharon
Subject: STN125085/91 - Information request

Lisa,

We have the following question for Genentech:

In the efficacy dataset IRFPAT.xpt, 'lost to follow-up' was flagged by variable PFSLOSTR. The first reason for lost to follow-up is that 'Patient did not die within 84 days of last treatment prior to efficacy cutoff and had a last tumor evaluation 168 days or more after efficacy cutoff'. Please explain why a 'last tumor evaluation 168 days or more after efficacy cutoff' is needed in this reason.

Please reply by Thursday, Dec 12.

Thanks.

Lee

Record of Telephone Conversation

BLA STN125085/91
IND Sponsor Genentech
To File
From Lee H. Pai-Scherf, MD *LHP-S*
Subject Comments on FDA briefing book for ODAC
Date November 28, 2007
Initiated By FDA
Contact Phone 650-225-3512
FDA Participant(s) Lee H. Pai-Scherf, MD,
Non-FDA Participant (s) Lisa Bell

Summary of Teleconference:

Genentech submitted a request for correction and suggestions for revision to FDA's briefing book for December 5, 2007 ODAC.

Genentech disagreed with the following statement in the FDA's briefing book, Regulatory History, page 3: "The FDA again expressed concerns regarding the open-label trial design and requested an independent radiology review for confirmation of the progression events". Genentech stated that neither the FDA nor Genentech's minutes from the September 28, 2005 pre-sBLA meeting reflected this request.

FDA acknowledged that the recommendation for an independent review was not specifically captured in the written minutes for that particular meeting, however the need for an independent review, the concern regarding the unblinded nature of the study and lack of pre-specified parameters to determine disease progression in the E2100 study were communicated to NCI and Genentech in previous letters and meetings.

Ms. Bell agreed that that appears to be the case. (It was noted that neither Ms. Bell nor Dr. Pai-Scherf were present at those early meetings, but both agreed, by reading all the communications between FDA, NCI and Genentech, that the need for an independent review was clear).

Genentech also provided several suggestions for revisions and clarifications to the FDA's briefing book. Given that the proposed revisions were minor and would not change the meaning or content of the briefing document, FDA would not issue an errata. Genentech agreed.

Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Wednesday, November 28, 2007 9:47 AM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon; Lu, Hong (Laura)
Subject: ~~STN125085/91~~ - Information Request

Lisa,

In the E2100 study 63 (8.7%) of the patients had bone disease only. We would like to know the PD status of these patients. Please flag these patients in the IRFPAT.xpt. file so we can conduct this analysis.

Please forward this information to me no later than Monday, Dec.3.

Thanks.

Lee

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
ODDP/CDER/FDA
WO22, Rm 2314
301-796-1430

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Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Wednesday, October 24, 2007 10:20 PM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon
Subject: STN#2505/91. E2100: Information request Patient ID

Lisa,

Patient 28059 is listed as one of the patients in the PAC/BV arm with AE (constitutional) that resulted in death.

Review of the case report form indicates that this patient was admitted on _____ with shortness of breath, grade 3 hypertension, weakness. She was discharged home on ____ "recovered/resolved without sequela". The patient died the day after she was sent home. Cause of death is listed as disease progression. **b(6)**

This patient has bone metastasis and ECOG disease evaluation form states that she has stable disease on August 5, 2004.

Case narratives states "the constitutional symptoms were assessed as unrelated to bevacizumab and definitely related to breast cancer and brain metastasis"

I'm unable to find evidence of progressive disease based on the CRF and the information provided. Please forward to me the information to support the cause of death as disease progression and brain metastasis.

Thanks.

Lee

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
ODDP/CDER/FDA
WO22, Rm 2314
Ph 301-796-1430

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Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Wednesday, October 24, 2007 10:06 PM
To: Sickafuse, Sharon
Subject: FW: STN125085/91 Information Request: SAS variable

FYI, forgot to cc you earlier.

From: Pai-Scherf, Lee
Sent: Wednesday, October 24, 2007 2:26 PM
To: 'Lisa Bell'
Subject: STN125085/91 Information Request: SAS variable

Lisa,

142 patients (19.7%) discontinued therapy due to toxicity/side effects/complications. Please provide in a tabular format, the toxicity(s) leading to discontinuation of the treatment.

Please provide me (or, if already in the submission point out to me) the SAS variable where this information can be found.

Please provide me with the information as soon as possible.

Lee

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
OODP/CDER/FDA
WO22, Rm 2314
Ph 301-796-1430

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Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Wednesday, October 24, 2007 10:05 PM
To: Sickafuse, Sharon
Subject: FW: STN125085/91 Querie: AVF2119g: OS

Attachments: Picture (Metafile)

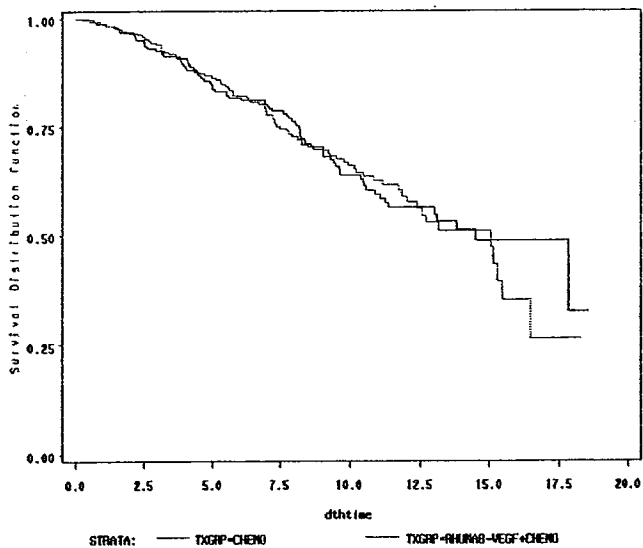
From: Pai-Scherf, Lee
Sent: Wednesday, October 24, 2007 2:37 PM
To: 'Lisa Bell'
Subject: STN125085/91 Querie: AVF2119g: OS

Lisa,

The are trying to verify Genentech's OS results for AVF2119g, but the pat2119.xpt contain information for only 444 patients, but there are 462 patients reported in the OS results table in the CSR.

Please explain the difference and if you can provide us with the complete data set?

Lee



	Capecitabine Alone (n=215)	rhuMAb VEGF + Capecitabine (n=229)
Subjects who died as of 28 June 2002	82	85
Censored observations	133	144
Unstratified analysis		
Hazard ratio c	—	1.04
95% CI	—	(0.77, 1.41)
p-value (log-rank)	—	0.785

Sickafuse, Sharon

m: Pai-Scherf, Lee
at: Tuesday, October 23, 2007 7:46 PM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon
Subject: STN 125085/91 E2100 Information Request: Stratification factor

Lisa:
Please provide me with the patient distribution by stratification factors as shown in the following table. Please specify how the information was collected for each factor.

ITT population Distribution by stratification factors

Stratification Factor		PAC (N, %)	PAC/BEV (N, %)
Disease-free interval	≤ 24 months		
	> 24 months		
Number of metastatic sites	< 3		
	≥ 3		
Prior adj. chemo	Yes		
	No		
ER status	Positive		
	Negative		
	Unknown		

Please forward to me the information by Friday, October 26.

Thanks.
Lee

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
OODP/CDER/FDA
WO22, Rm 2314
Ph 301-796-1430

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Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Sunday, October 21, 2007 10:52 PM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon; Lu, Hong (Laura)
Subject: STN 125085/91 E2100: Please confirm FDA findings

Lisa,

I would like for Genentech to confirm the following concordance/discordance of PFS and response between ECOG and IRF findings below (Table 1-4).

Please send me your response no later than Friday, October 26.

Thanks.

Lee

Table 1. Concordance/Discordance between IRF and ECOG in PFS Event Status

Treatment Arm	Number of Discordance (%)	Number of concordance (%)
PAC	84 (23.7%)	270 (76.3%)
PAC/BEV	90 (24.5)	278 (75.5%)
Total	174 (24.1%)	548 (75.9)

Table 2. Concordance/Discordance between IRF and ECOG in PFS Date

Treatment Arm	Number of Discordance (%)	Number of concordance (%)
PAC	181 (51.1%)	173 (48.9%)
PAC/BEV	187 (50.8%)	181 (49.2%)
Total	368 (51.0%)	354 (49.0%)

Table 3. Concordance/Discordance between IRF and ECOG in Response Status

Treatment Arm	Number of Discordance (%)	Number of concordance (%)
PAC	64 (18.1%)	290 (81.9%)
PAC/BEV	88 (24.5)	280 (75.5%)
Total	152 (24.1%)	570 (75.9%)

Table 4. Concordance/Discordance between IRF and ECOG in Earliest Response Date

Treatment Arm	Number of Discordance (%)	Number of concordance (%)
PAC	79(22.3%)	275 (77.7%)
PAC/BEV	117 (31.8%)	251 (68.2%)
Total	196 (27.1%)	526 (72.9%)

Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Sunday, October 21, 2007 10:42 PM
To: 'Lisa Bell'
Cc: Lu, Hong (Laura); Sickafuse, Sharon
Subject: STN125085/91 E2100 Information Request: Missing data

Dear Lisa,

1. Table 14.2/19 of the E2100 CSR shows the Completely Missing Radiograph Images by Visit per IRF (randomized patients with at least one scan available to the IRF). Please confirm that the group of 'Patient Expected to have a Radiographic Assessment' excludes patients who had no scan available to the IRF, had started NPT, had progression or died before 2/9/2005.

2. For Table 14.2/24a of the E2100 CSR entitled "PFS per IRF: Missing Data Analysis 4 Randomized Patients", please provide the SAS program t_irf_missresp

Please provide me with this information no later than Wednesday, October 24.

Thanks.

Lee

Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Wednesday, October 17, 2007 10:36 AM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon; Lu, Hong (Laura)
Subject: STN 125085/91 E2100 Information Request: Progression by ECOG

Lisa.

In the PAT.xpt dataset, ECOG determined progression, please provide an indicator for either clinical or radiographic progression as determined by ECOG.

Please provide the information above no later than Monday, October 22.

Thanks.

Lee

Sickafuse, Sharon

From: Pai-Scherf, Lee
nt: Tuesday, October 16, 2007 1:50 PM
U: 'Lisa Bell'
Cc: Sickafuse, Sharon; Lu, Hong (Laura)
Subject: STN125085/91: E2100 Information Request: ECOG/IRF concordance

Lisa:

ECOG and IRF were discordant on the status of PFS events on 174 (84 in PAC arm and 90 in PAC/BEV arm) patients out of the 722 patients in Study 2100. Among those patients whose event status was agreed by ECOG and IRF, 194 of them (97 in PAC arm, 97 in PAC/BEV arm) do not have the same date of PFS by ECOG investigator and IRF. For example, patient #21060's NPT stating date was 25FEB2003, and the PD date was 07FEB2003 by both ECOG and IRF. But ECOG treated this patient as censored and IRF treated the patient as a PD event. Please provide reasons for the above differences.

Please send reply to me no later than Friday, October 19.

Thanks.

Lee

Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Friday, October 12, 2007 7:10 PM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon
Subject: STN 125085/91 - E2100 Information Request: Narratives

Lisa,

1. I have reviewed the CRF and case narratives of patients in the PAC/BEV arm with death attributed to "due to other cause" or "unknown". In this group, four patients (21403, 22025, 26004, 21390) died of MI, CHF or sudden death at home. One patient (23012, EPP) had grade 3 CHF, but no follow up information is provided. If possible, please provide the past medical history for these patients and follow up information for 23012 (death? recovered?). I'm specifically interested in predisposing factors that might help explain these deaths. Any baseline ECG or MUGA/ECHO will also be helpful.

2. In order to have a balanced assessment for both arms in the study, I'm requesting case narrative for the following patients in the PAC arm: 21284, 26030, 26024 (died within 1, 14 and 24 days after therapy with cause attributed to "other" or "unknown").

Please provide me with this information no later than Wednesday, October 17.

Thanks.

Lee

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
OODP/CDER/FDA
WO22, Rm 2314
Ph 301-796-1430

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Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Wednesday, October 10, 2007 2:51 PM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon; Lu, Hong (Laura)
Subject: STN 125085/91 Information Request: E2100 PFS analysis

Lisa:

We have the following request for clarification and information:

1. In the derived dataset IRFPAT, 46 clinical progressions are identified by the variable CLINPROG. Among the 324 progression events identified by the variable PFSTYPER, are the remaining 278 (324-46) events due to radiographic progression? If not, please provide a revised dataset to specify how progression was determined and flag those events due to radiographic progression.
2. Tables 14.2/4 and 14.2/31 of the CSR present the result of subgroup analysis for PFS and OS. Please provide the number of events for each treatment arm and each subgroup.

Please provide me with the above information no later than Friday, October 12.

Thanks.

Lee

Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Monday, October 08, 2007 11:36 PM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon
Subject: STN 125085/91, E2100 - Information request

Lisa,

I'm having difficulties cross matching the case narratives provided in section 16.5 with specific patients in the SAS data set and the following tables.

For Table 14.3/26, please provide the patient ID # for the patients who died due to protocol treatment (1 case for PAC), due to other cause (7 PAC and 9 PAC/BV) and unknown (7 in PAC arm, 3 in PAC/BV). Please also indicate if case narratives are available for all patients.

Table 14.3/27, please provide ID # for all the patients and attribution with deaths within 30 days of the last study treatment (PAC 2, PAC/BV 6).

Table 14.3/28 shows all NCI-CTC AEs that resulted in death. Please provide the ID # of all patients on this table (7 in PAC arm, 11 in PAC/BV arm), please specify cause of death as in the table, i.e., constitutional, cardiovascular (ischemia, other, LVF, sinus bradycardia), gastrointestinal (colitis, GI other, hepatic), infection/neutropenia, pulmonary, renal, syndromes). Please also indicate if narratives are provided for all the patients.

Table 14.3/32 reports selected grade 3-5 AEs by AdEERS or CRF. Please provide the ID # for individual patients (grade 5, 4 and 3) as shown in this table.

Please provide me with the above information no later than Friday, October 12.

Thanks.

Lee

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Friday, September 28, 2007 4:35 PM
To: 'Lisa Bell'
Subject: FW: STN 125085/91.018 - Query

From: Pai-Scherf, Lee
Sent: Friday, September 28, 2007 4:01 PM
To: Sickafuse, Sharon
Subject: STN 125085/91.018 - Query

Sharon:

Please forward the following question to Genentech regarding E2100:

The E2100 Audit Certification Listing per CTEP, NCI (Section 16.1.8 of CSR) indicates that total Enrollment on E2100 trial is 720 patients.

The E2100 CSR and the datasets submitted all indicate that 722 patients were enrolled. Please clarify the discrepancy.

Lee

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
OODP/CDER/FDA
WO22, Rm 2314
Ph 301-796-1430

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Sickafuse, Sharon

From: Pai-Scherf, Lee
Sent: Sunday, September 23, 2007 3:22 PM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon
Subject: FW: STN 125085-91.018 - Information Request

Importance: High

Lisa,

Regarding my Friday's request, I was able to locate the RadPharm imaging and oncology assessment in the CRF file for individual patients, including the DCFs. I was looking for them in the wrong place. Thus my previous request for this is cancelled.

I still would like to have the overall missing scan report Genentech received from Rad Pharm (if it is already submitted, please point out where I can find it).

Thanks.

Lee

From: Pai-Scherf, Lee
Sent: Friday, September 21, 2007 12:42 PM
To: Sickafuse, Sharon
Cc: Keegan, Patricia
Subject: STN 125085-91.018 - Information Request
Importance: High

Sharon,

Please request Genentech to submit the following information:

1. all Source Documents (locked dataset) Genentech received from RadPharm for E2100 imaging and oncology assessment. Please include all DCFs (data clarification forms) used to maintain the audit trail for any changes to the "locked data set".
2. Missing scan report received from Rad Pharm.

We would like to have this information no later than September 26.

Thanks.

Lee

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
CDOP/CDER/FDA

Sickafuse, Sharon

From: Sickafuse, Sharon
sent: Friday, September 21, 2007 12:56 PM
to: 'Lisa Bell'
subject: STN 25085/91 - Information Request
Importance: High

Hi Lisa,

Please submit the following information:

1. All Source Documents (locked dataset) Genentech received from RadPharm for E2100 imaging and oncology assessment. Please include all DCFs (data clarification forms) used to maintain the audit trail for any changes to the "locked data set".
2. Missing scan report received from Rad Pharm.

We would like to have this information no later than September 26.

Thank you

Lee Pai-Scherf, MD
Medical Officer
Division of Biologic Oncology Products
OODP/CDER/FDA
WO22, Rm 2314
Ph 301-796-1430

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SEP 06 2007

Our STN: BL 125085/91

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

Dear Dr. Rich:

We have received your August 23, 2007, resubmission to your supplement to your biologics license application for Bevacizumab on August 24, 2007.

The resubmission contains additional clinical information that you submitted in response to our September 8, 2006, complete response letter.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is February 23, 2008.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Ms. Sharon Sickafuse, at (301) 796-2320.

Sincerely,

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125085/91

JUL 9 1 2007

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

Dear Dr. Rich:

This letter is in regard to the supplement to your biologics license application for Bevacizumab submitted under Section 351 of the Public Health Service Act.

We have reviewed your May 15, 2007, submission which contained a supplemental statistical analysis plan (SAP) and a revised Independent Review Facility (IRF) charter for study E2100. The supplemental SAP contains additional analytic plans regarding missing data in the analysis of progression-free survival (PFS). We have the following comments:

Regarding the SAP:

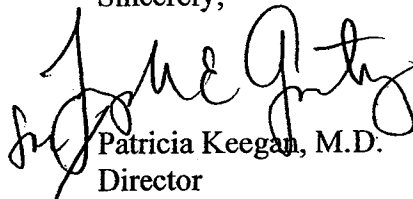
1. Please provide the number and percentage of patients missing at baseline and each **post-baseline visit** for "completely missing radiographic images" and "missing time point responses."
2. Section 5.2 of your submission states that in the primary analysis for PFS, "When a timepoint assessment of PD is immediately preceded by a time point assessment of UE, the date of progression will be backdated by the oncologist reader for the overall read to the date of the previous UE assessment." Please clarify whether the PD event will be backdated if the radiographic images immediately preceding the event are completely missing.

Regarding the IRF Charter:

3. The charter states that the Chief Medical Officer reviews the test case performance of the new radiologist(s), and qualifies him or her according to RadPharm Standard Operating Procedures (SOPs). It is not clear as to what criteria will be utilized to determine the necessity to re-train or replace the reviewers. Therefore, we recommend that you predefine an acceptable proficiency level for the qualification of radiologists to serve as readers for this trial.

If you have any questions, please contact Ms. Sharon Sickafuse, Regulatory Project Manager, at (301) 796-2320.

Sincerely,

A handwritten signature in black ink, appearing to read "Patricia Keegan". The signature is fluid and cursive, with a large initial "P" and "K".

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125085/91

JUL 3 0 2007

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

Dear Dr. Rich:

This letter is in regard to the supplement to your biologics license application for Bevacizumab submitted under Section 351 of the Public Health Service Act.

We have reviewed your April 4, 2007, submission which contained a revised statistical analysis plan (SAP) for study E2100 submitted in response to our letter of February 12, 2007. Your April 4, 2007, submission makes the following revisions to the SAP:

1. A proposal to perform an analysis for overall survival based on 481 events. This analysis will constitute full information for survival.
2. An acknowledgement that Quality of Life analyses will be considered exploratory.

The above revisions are acceptable.

If you have any questions, please contact Ms. Sharon Sickafuse, Regulatory Project Manager, at (301) 796-2320.

Sincerely,


Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Memorandum

Date ~~05/20/2007~~

From Lee Pai-Scherf, MD, Medical Officer *L.P.S.*
DBOP/OODP/CDER/FDA

To: STN ~~125085/91~~

Re: Review of May 9, 2007, submission

Background: STN 125085/91 was submitted by Genentech on May 23, 2006, for the expansion of product labeling to include Avastin® in combination with paclitaxel chemotherapy for first-line treatment of patients with locally recurrent or metastatic breast cancer. A Complete Response letter for this supplement was issued by the FDA on September 8, 2006. Reference is made to a teleconference held between Genentech and FDA on March 22, 2007, where Genentech agreed to provide further information regarding the eligibility data that will support the resubmission of Study E2100.

The May 9, 2007, submission contains a summary of the ECOG process for review of eligibility as requested by the FDA and Genentech's proposal for submission of eligibility data for the E2100 sBLA resubmission.

Genentech proposes to submit the following eligibility information:

- Electronic copies of eligibility checklists for all subjects. It is noted that the checklist was designed as a worksheet and was not reviewed or cleaned by ECOG's data specialist.
- Genentech will include tabular summaries (including dataset) of the screening laboratory values captured on the checklist of all patients
- E2100 case report forms which includes key eligibility criteria identified and captured by ECOG. It is noted that E2100 case report forms did not include non-breast cancer past medical history, concomitant medications, and laboratory values.

The following request for clarification and comment was forwarded to Genentech via electronic mail on June 7, 2007. Genentech replied via e.mail on June 12, 2007.

1. Please clarify how inconsistencies (if any) between the checklist and the CRF will be reconciled. Please provide hyperlinks to all queries.

Genentech's Response: The elements captured on the Case Report Form were reviewed by the ECOG Data Coordinating Center. If there was any missing information or inconsistencies with the requirements of the protocol these were queried back to the site. If the data reported was verified as accurate, and verified by the study chair as inconsistent with the requirements of the protocol, the patient was deemed ineligible. The Data Correction Forms were collected and will be included in the submission with hyperlinks to the original CRF as appropriate. The checklists were used as a screening document by the site. Post randomization, any inconsistency in the key eligibility information for a subject was determined thru the use of the case report form as described above.

2. The eligibility dataset should provide information regarding the document source for every eligibility factor (i.e., checklist, CRF, both or other)

Genentech's Response: This information will be provided in the data tipsheet in the submission

On June 12, 2007, Genentech was informed via electronic mail that the proposal for submission of eligibility data for E2100 is acceptable.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125085/91

MAR 05 2007

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

Dear Dr. Rich:

This letter is in regard to the supplement to your biologics license application for Bevacizumab submitted under Section 351 of the Public Health Service Act.

We also refer to your January 26, 2007, amendment which contained a request for a revision of the minutes from the November 2, 2006, meeting regarding the discussion surrounding Genentech's question 12: *"Does the Agency agree with Genentech's proposal to submit the eligibility checklist information? If so, does the Agency agree with Genentech's proposal to provide eligibility checklists and CRFs for all 722 patients enrolled in Study E2100?"*

In FDA's draft responses to your questions which were provided to you on November 1, 2006, we stated that your proposal was acceptable and that queries, corrections, and their explanations must be provided via hyperlink in the CRF.

The minutes of the November 2, 2006, meeting state the following: "ECOG clarified that the eligibility checklist form from the investigational sites is a working form and is not always accurate or complete. ECOG's internal forms are more accurate, however ECOG's review does not include an assessment of all factors required to verify eligibility (e.g., review of laboratory values). ECOG will work with Genentech to provide eligibility checklists on all 722 patients which will be converted to pdf files and provided in the resubmission. This is acceptable to the FDA."

In your request for a revision of the minutes, you state that during the meeting, FDA was informed that the eligibility checklist is not a formal CRF and that the ECOG eligibility form is cleaned and checked, whereas the checklist is not. You stated that Genentech asked FDA if we still wanted to receive the checklist in the resubmission and FDA said no.

For clarity, we are revising the meeting minutes as follows:

ECOG clarified that the eligibility checklist form from the investigational sites is a working form and is not always accurate or complete. ECOG's internal forms are more accurate, however ECOG's review does not include an assessment of all factors required to verify eligibility (e.g., review of laboratory values). ECOG will work with Genentech to provide eligibility information on all 722 patients which will be provided in the resubmission. This is acceptable to the FDA. Given the poor data quality of the checklist forms from investigational sites, the FDA will not require submission of the checklists, but assessment of all factors required to verify patient eligibility on all 722 patients, including review of laboratory values must be included in the submission.

If you have any questions, please contact Ms. Sharon Sickafuse, Regulatory Project Manager, at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Enclosure: Revised Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 2, 2006
APPLICATION: STN 125085/91
SPONSOR: Genentech, Incorporated
DRUG NAME: Bevacizumab
INDICATION: First-line treatment of locally recurrent or metastatic breast cancer
TYPE OF MEETING: Type A

MEETING RECORDER: Sharon Sickafuse

FDA ATTENDEES:

Office of Oncology Drug Products

Richard Pazdur, M.D.

Karen Weiss, M.D.

Division of Biologic Oncology Products

Joe Gootenberg, M.D.

Karen Jones

Patricia Keegan, M.D.

Steven Lemery, M.D.

Lee Pai-Scherf, M.D.

Kaushik Shastri, M.D.

Sharon Sickafuse, M.S.

Jeff Summers, M.D.

Office of Biostatistics

Division V

Laura Lu, Ph.D.

Mark Rothmann, Ph.D.

Office of the Commissioner

Office of Special Health Issues

Patricia Delaney

Blair Schwartz

Erin Robey

Melissa Vogel

SPONSOR ATTENDEES:

Genentech, Inc.

Alex Bajamonde, Ph.D., Director of Biostatistics
Lisa Bell, Ph.D., Associate Director, Regulatory Affairs
Gwen Fyfe, M.D., Vice President, BioOncology
Barbara Klencke, M.D., Senior Medical Director, BioOncology
Chandra Lovejoy, Manager, Regulatory Affairs
Bob Mass, M.D. Principal Medical Director, BioOncology
Michael Ostland, Ph.D., Associate Director, Biostatistics
Todd Rich, M.D., Vice President, Regulatory Affairs
David Schenkein,
Xiaolin Wang, Sc.D., Associate Director, Biostatistics
Kathie Winson,
Bei Yao Zheng, Ph.D., Senior Statistical Scientist, Biostatistics

NCI/CTEP:

Jeff Abrams, M.D., Associate Chief – Medicine, Clinical Investigations Branch
Helen Chen, M.D., Senior Investigator, Investigational Drug Branch
Michaele Christian, M.D., Associate Director
Sally Hunsberger,
JoAnne Zujewski, M.D., Senior Investigator, Breast Cancer Therapeutics, Clinical Investigations Branch

Eastern Cooperative Oncology Group (ECOG):

Robert Comis, M.D., Group Chair
Robert Gray, Ph.D., Group Statistician
Deidre Levine,
Donna Maranucci,
Kathy Miller,
Mary Steele,

BACKGROUND: The NCI submitted study E2100, “A Randomized, Phase 3 Trial of Paclitaxel Versus Paclitaxel Plus Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer” to IND 7921 on October 18, 2001. The protocol was submitted to the FDA before the NCI Central IRB’s September 18, 2001, required revisions were incorporated. Those revisions were subsequently made and a revised protocol was submitted to IND 7921 on November 14, 2001.

The protocol background information in the November 14, 2001 submission described prior experience with Bevacizumab in Study AVF0776g, “An Open-label, Dose-ranging, Phase 2 Study of Single Agent Avastin Conducted in Women Receiving Second-line Treatment for Metastatic Breast Cancer.” The background section contained no references to Genentech’s AVF2119g Phase 3 study of Bevacizumab in breast cancer. Study AVF2119g completed accrual in November 2001 and negative results were released on September 9, 2002.

During the November 20, 2001, teleconference requested by Genentech to discuss the results of a Phase 2 trial conducted by NCI to support labeling expansion for another indication (not breast cancer), FDA requested that Genentech provide clarification of their overall Bevacizumab development strategy and the role of NCI trials in that development strategy. Genentech agreed to provide a compendium of ongoing trials and an updated Bevacizumab development plan focusing on registration trials and proposed timelines. Genentech submitted their response to FDA's request to IND 7023 on March 14, 2002, identifying E2100 and two additional trials being conducted under NCI's IND 7921 as "non-Genentech trials intended to support a possible license application." Subsequent to receipt of this information, FDA communicated concerns to NCI regarding the protocol design and data collection for study E2100 in a series of letters, beginning on May 2, 2002.

The results of E2100 were analyzed by ECOG, with initial public release on April 14, 2005, presented at the May 2005 ASCO meeting, and submitted as an amendment to Genentech's IND 7023 on August 25, 2005, as part of the meeting package for the pre-sBLA meeting held September 28, 2005. During the pre-sBLA meeting, Genentech posed the following question:

"... Genentech believes that the highly significant PFS results, a trend in overall survival, and the safety profile observed with Bevacizumab in Study E2100 are sufficient to support an sBLA to extend the current indication of Avastin to the following: _____

_____ ' Does the Agency agree that this study can form the basis for this sBLA?"

b(4)

The efficacy results provided in the August 25, 2005, submission included an improvement in overall response rate (14.2% vs. 28.2%, $p < 0.0001$) and an encouraging comparison in overall survival (HR=0.674, log-rank test, $p = 0.01$).

The importance of the results on overall survival to the review of this application were further clarified in FDA's response to the following question, posed by Genentech during the September 28, 2005 meeting:

"Given the strength of the PFS data and the known safety profile of Bevacizumab, does the Agency agree that...The data will support full approval?"

FDA's response provided to Genentech prior to the September 28, 2005, meeting stated: "No. The endpoint of PFS will support an accelerated approval. At the time of filing, please submit data on overall survival. Mature data concerning overall survival will be requested as a post-marketing commitment and will convert the sBLA from accelerated approval to full approval."

The meeting minutes generated by FDA captured the following additional discussion:

"Genentech noted that cross-over was not allowed in study E2100. Since the public release of information concerning E2100, ECOG has not noted an increase in the number of patients in

the control arm who discontinue paclitaxel (with or without progression) and then initiate chemotherapy plus commercially available Bevacizumab.”

On May 23, 2006, Genentech submitted a sBLA for study E2100. In contrast to the “trend in overall survival” described at the September 28, 2005, meeting, the updated survival information contained in the efficacy supplement showed an erosion of the effect and raised concern about the effect on overall survival suggested by the earlier analyses (HR=0.821, p=0.082 stratified log-rank). FDA issued a letter on July 21, 2006, filing the supplement and identifying deficiencies. On September 8, 2006, FDA issued a complete response (CR) letter.

On September 29, 2006, Genentech submitted a request for a type A meeting to discuss the September 8, 2006, CR letter. The meeting package was submitted on October 18, 2006. Draft FDA responses to Genentech’s questions were provided to Genentech on November 1, 2006.

MEETING OBJECTIVES: Discuss how Genentech can best address the September 8, 2006, CR letter and how to ensure that the content of their response addresses the most important review issues.

Genentech opened the meeting with the following new proposals (not described in the meeting package):

New Safety Data Proposal:

Rather than provide all safety data (including MedWatch and AdEERS forms) identified as occurring on or before the data cut-off date of February 9, 2005, as stated in the meeting package, Genentech now proposed to include all safety data through August 2005. Genentech justified this proposal based on the following information:

As of August 2005, only 42 patients were still receiving treatment (35 on the Bevacizumab arm and 7 on the control arm). Ninety-four percent of all patients registered and randomized have completed all protocol treatment and safety data collection (excluding survival information). Genentech stated that 7 additional AdEERS reports have been generated for events occurring after August 9, 2005.

FDA expressed concerns with this proposal particularly for AdEERS reporting, given that measurable levels of Bevacizumab are present for at least 6 months after the last dose. FDA expressed a preference for a later cut-off date for serious adverse events (AdEERS/MedWatch reports); Genentech proposed and FDA agreed that inclusion of all AdEERS reports through October 7, 2006, was acceptable. In addition, FDA stated that February 9, 2005, would not be an acceptable cut-off date for survival data.

This issue of the data cut-off date for survival information remains outstanding.

Progression Free Survival (PFS) Endpoint Validation Proposal:

In response to FDA's draft responses provided to Genentech on November 1, 2006, Genentech stated at the meeting that they will perform an independent review to validate the primary endpoint of PFS in all 722 patients using the modified RECIST criteria. The independent review facility (IRF) will receive all imaging scans as well as pertinent clinical data. Genentech will perform due diligence to collect scans on all 722 patients and anticipates that they will have collected more than 90% of the scans by the end of March 2007.

FDA stated that Genentech's proposal for an independent review of all patient films, with PFS determined using the modified RECIST criteria was acceptable. Genentech will submit the IRF charter to FDA for review and comment.

Genentech stated that they will make the following revisions to the statistical analysis plan (SAP) which will be submitted to FDA:

- The primary analysis is based on IRF data.

FDA agreed with this revision.

- The definition of PFS will be amended to not include deaths that occurred greater than _____ after the last treatment.

b(4)

FDA recommended that the definition of PFS be amended to censor at the date of the last study visit those patients whose deaths occurred more than 84 days after the last treatment. Genentech agreed to do this.

Genentech proposed not to include images in the sBLA resubmission, however films would be available upon request. FDA agreed with this proposal.

SPONSOR QUESTIONS AND FDA RESPONSES:

1. *Genentech believes that endpoint validation is a central issue of our recent complete response letter. What data should be included in this submission to ensure that the Agency can assess the adequacy of this trial for approval?*

FDA Response:

Endpoint validation is one of the many issues of the CR letter. The lack of a locked data set with ongoing data collection and clean up made it impossible for the FDA to assess the conduct of the study and the efficacy and safety of your claim.

Justification of the sample size for endpoint validation must be based on the projected number, direction, and magnitude of the discordant readings between the investigator and the masked, external review for outcomes.

Discussion: See Progression Free Survival (PFS) Endpoint Validation Proposal above. FDA agreed that a re-analysis of PFS by an independent review committee that included more than 90% of the patients was acceptable.

2. *Genentech would like to request specific guidance as to what would enable inclusion of the progression-free survival (PFS) hazard ratio and medians and objective response rate in the label?*

FDA Response:

Genentech must provide data that demonstrates that the investigator assessed response is reliable based on an independent endpoint validation and the April 5, 2005, SAP which FDA has indicated is acceptable. FDA is willing to discuss this issue further pending submission of the IRF findings.

Discussion: See Progression Free Survival (PFS) Endpoint Validation Proposal above.

3. *Genentech proposes to include preliminary overall survival information in the label. Does the Agency agree?*

FDA Response:

We are unable to comment on the label at this time. However, inclusion of an unplanned analysis is unlikely. All analyses must be consistent with the accepted pre-specified SAP of April 4, 2005.

Discussion: Genentech stated that the final analysis of survival is not expected to occur until November 2007. The final overall survival analysis will be completed when there are 481 events. The SAP did not provide any plans for interim analyses of survival. For the purposes of safety, not for demonstrating efficacy, FDA requested that an unplanned interim analysis of survival be provided in the resubmission. The cut-off date for this interim analysis was not agreed upon at the meeting, however FDA stated that this information is important in characterizing safety and is critical to the review of the resubmission. FDA stated and Genentech acknowledged that formal comparison from an unplanned interim analysis of survival cannot be included in product labeling.

4. *To ensure that the intent of the complete response letter is met, Genentech requests that the Agency clarify whether there are any other review issues involving new data that Genentech should consider in working with ECOG on the resubmission.*

FDA Response:

Additional review issues might arise during the review of your resubmission.

Discussion: FDA clarified that it has no additional concerns that were not already stated in the September 8, 2006, CR letter, however new issues may arise as a result of the new information to be provided in the resubmission.

5. *Does the Agency agree with Genentech's proposal for the content and format of the sBLA resubmission of the clinical study report, patient narratives, case report forms (CRFs), and case report tabulations?*

FDA Response:

Yes. The overall content is acceptable.

Discussion: None.

6. *Does the Agency agree with the methodology used for applying the cutoff date of February 9, 2005?*

FDA Response:

The cut-off date of February 9, 2005, is acceptable for the primary efficacy analysis. However, for safety and survival, the cut-off date should be no earlier than October 2006. The data that has been submitted in accordance with the ECOG-specified timeframes for data reporting should be provided. We note that more than 2 years will have elapsed since the February 2005 cut-off and the proposed resubmission.

Discussion: FDA restated that a cut-off date of February 2005 for tumor assessments (PFS) is acceptable. Genentech noted that the original submission contained all survival data received as of December 2005 and proposed to provide data on all deaths occurring on or before February 2005. FDA did not agree with Genentech's proposal and stated that all survival data through October 2006 (cleaned) or through March 2007 (data submitted, but not verified to be 100% complete or accurate) must be provided. NCI and ECOG argued that collection of interim survival information is time consuming and would require strenuous resources that are unnecessary for the sBLA resubmission. FDA strongly disagreed, noting that the request would be based on data captured on a single CRF and restricted to the single element of survival status. Although interim analysis of survival data was not pre-specified in the analysis plan for efficacy, FDA strongly recommended that Genentech provide up-to-date survival information at the time of sBLA resubmission as part of the safety analysis. FDA will not review and will not approve an efficacy supplement based on survival information that lacks data collected over a 2-year period.

Regarding the cut-off date for safety, see the New Safety Data Proposal above.

7. *Genentech proposes to submit a _____ that would include new events reported during the period between _____ Does the Agency agree with the proposal for the _____ as described?*

b(4)

FDA Response:

No. Please refer to our answer to your question #6 above.

Discussion: FDA agreed that because all serious adverse events through October 2006 will be provided in the resubmission and all other adverse events through August 2005 were provided in the original submission, a 120 day safety update need not be submitted during the resubmission review period.

Regarding Comment 1 in the September 8, 2006, CR letter:

8. *Is the data cutoff date of 9 February 2005 for the resubmission acceptable to the Agency?*

FDA Response:

No. Please refer to our answer to your question #6 above.

Discussion: This was addressed in response to previous comments/questions.

Regarding Comment 2 in the September 8, 2006, CR letter:

9. *Does the Agency agree with Genentech's proposal to conduct the IRF review using a charter based on the modified Response Evaluation Criteria in Solid Tumors (RECIST)?*

FDA Response:

No. As discussed during the teleconference of August 2, 2006, and in our email to your of August 30, 2006, the IRF review must be conducted using the same criteria as the investigator was required to use during the conduct of the study. The IRF review can use Genentech's proposed modified criteria if the review is conducted in all 722 patients enrolled in the study.

Discussion: This was addressed in response to previous comments/questions. See Progression Free Survival (PFS) Endpoint Validation Proposal above.

10. *Can the Agency provide further specific guidance as to the evidence required to warrant inclusion of the PFS hazard ratio and point estimate for the medians as well as the response rates in the label?*

FDA Response:

Please refer to our answer to your question #2 above.

Discussion: This was addressed in response to previous comments/questions.

11. *Genentech believes that endpoint validation is a central issue of our recent complete response letter. What data should be included in the submission to ensure that the Agency can assess the adequacy of this trial for approval? In particular, Genentech requests clarification from the Agency as to whether the confidence interval approach is appropriate for sample size justification. In addition, Genentech requests feedback from the Agency as to the sample size sufficient for endpoint verification.*

FDA Response:

Please refer to our answer to your question #1 above.

Discussion: This was addressed in response to previous comments/questions.

Regarding Comment 3 in the September 8, 2006, CR letter:

12. *Does the Agency with Genentech's proposal to submit the eligibility checklist information? If so, does the Agency agree with Genentech's proposal to provide eligibility checklists and CFRs for all 722 patients enrolled in Study E2100?*

FDA Response:

Yes. Queries, corrections and their explanations must be provided via hyperlink in the CRF.

Discussion: ECOG clarified that the eligibility checklist form from the investigational sites is a working form and is not always accurate or complete. ECOG's internal forms are more accurate, however ECOG's review does not include an assessment of all factors required to verify eligibility (e.g., review of laboratory values). ECOG will work with Genentech to provide eligibility information on all 722 patients which will be provided in the resubmission. This is acceptable to the FDA. Given the poor data quality of the checklist forms from investigational sites, the FDA will not require submission of the checklists, but assessment of all factors required to verify patient eligibility on all 722 patients, including review of laboratory values must be included in the submission.

Regarding Comment 4 in the September 8, 2006, CR letter:

13. *Does the Agency agree with Genentech's proposal for providing dataset, ECOG Eligibility Evaluation Forms, and ECOG Case Evaluation Forms?*

FDA Response:

Yes.

Discussion: None.

Regarding Comment 5 in the September 8, 2006, CR letter:

14. *Does the Agency agree with Genentech's proposal to submit objective response information for all randomized patients with measurable and non-measurable disease?*

FDA Response:

Yes.

Discussion: None.

Regarding Comment 6 in the September 8, 2006, CR letter:

15. *Does the Agency agree with Genentech that it is not possible to quantify the extent of involvement for each non-target lesion?*

FDA Response:

Please note that comment #6 of the CR letter refers to non-measurable disease and not non-target lesions.

In addition to reporting the site of involvement for each non-measurable lesion, all descriptive information and verbatim information should be included in the resubmission.

Discussion: Genentech did not request clarification. Genentech will provide the data requested by FDA in the resubmission as follows: identification in the datasets of the site of the non-measurable lesion, the method used to characterize tumor response/progression, and the date of assessment. FDA requested, and Genentech agreed to provide, descriptive information regarding any assessment of disease progression/response at the non-measurable lesion site in a comment field.

16. *Does the Agency wish Genentech to instead report the site of involvement for each non-target lesion?*

FDA Response:

Please see comment #15 above.

Discussion: None.

17. *Does the Agency agree with Genentech's proposal for providing a listing for patients with non-measurable disease at baseline?*

FDA Response:

Yes.

Discussion: None.

Regarding Comment 7 in the September 8, 2006, CR letter:

18. *Genentech requests that the Agency confirm the acceptability of our response to collect no new data.*

FDA Response:

Yes, however failure to fully characterize some aspects of drug therapy may result in limitations in product labeling.

Discussion: Genentech expressed understand of the possible consequences of missing data.

Regarding Comment 8 in the September 8, 2006, CR letter:

19. *For the analysis of objective response, does the Agency agree with Genentech's proposal that the primary analysis population consist of patients with measurable disease at baseline, with a supporting analysis including all randomized patients?*

FDA Response:

Yes.

Discussion: None.

Regarding Comment 9 in the September 8, 2006, CR letter:

20. *Does the Agency agree with Genentech's proposal to provide information necessary to determine how patients with unevaluable or unknown response status were evaluated regarding PFS?*

FDA Response:

Yes. All descriptive, verbatim information should be included.

Discussion: None

Regarding Comment 10 in the September 8, 2006, CR letter:

21. *Does the Agency agree with Genentech's proposal to provide a summary of missing response assessments per timepoint as specified in the E2100 SAP of April 5, 2005?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 11 in the September 8, 2006, CR letter:

22. *Does the Agency agree with Genentech's proposal to provide comprehensive efficacy results for the interim analysis based on the February 9, 2005, database cut-off?*

FDA Response

Yes. It is FDA's understanding that this dataset and the analysis of disease-free survival will include all events occurring on or before February 9, 2005, and that all patients lost to follow-up prior to February 9, 2005, will be flagged. Genentech must also provide updated safety and survival data at the time of resubmission. Your proposal for censoring for overall survival is not acceptable. Patients who died past February 9, 2005, should be censored on this date, not the date of last follow-up.

Discussion: Genentech agreed to censor patients who died past February 9, 2005, on this date, not the date of last follow-up.

Regarding Comment 12 in the September 8, 2006, CR letter:

23. *Does the Agency agree with Genentech's proposal to provide a dataset as of the February 9, 2005, cut-off date that includes all of the variables in the current PATE.xpt dataset?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 13 in the September 8, 2006, CR letter:

24. *Does the Agency agree with Genentech's proposal not to include these SAS programs in our upcoming resubmission?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 14 in the September 8, 2006, CR letter:

25. *Does the Agency agree with Genentech's proposal to address the Agency's requests as presented in our response to item 14a of the September 8, 2006, complete response letter?*

FDA Response:

Given that height, weight, or BSA information were not collected by study sites, the proposed retrospective assumptions are acceptable.

Discussion: None

26. *Genentech requests that the Agency confirm that _____ is acceptable as the reason provided for a dose modification or omission.*

FDA Response:

Please provide the analysis and the dataset analysis program of adverse events occurring prior to or during any treatment cycle in which a _____ dose modification occurred.

Discussion: Genentech agreed to provide this information.

27. *Does the Agency agree with Genentech's proposal to provide a listing and tabulation for patients in the paclitaxel + Bevacizumab arm that include whether the dose modification or omission was planned or unplanned for each 3-cycle reporting period for each treatment arm?*

FDA Response:

Yes; however you should also provide additional analyses as described above in item #26.

Discussion: Genentech agreed to provide this information.

28. *Does the Agency agree with Genentech's proposal to address the Agency's requests as presented in our response to items 14c-14h of the September 8, 2006, complete response letter?*

FDA Response:

Yes.

Discussion: None

29. *Does the Agency agree with the proposed format and content for the narratives?*

FDA Response:

Yes.

Discussion: None

b(4)

Regarding Comment 15 in the September 8, 2006, CR letter:

30. *Does the Agency agree with Genentech's proposal to provide financial disclosure information for the Lead Principal Investigators for Study E2100?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 17 in the September 8, 2006, CR letter:

31. *Does the Agency agree with Genentech's proposal to provide _____ ?*

b(4)

FDA Response:

No. For each study site audited during the conduct of E2100, please provide a summary evaluation of the audit results. For sites with unacceptable findings, provide justification for inclusion of study data.

Discussion: NCI stated that full audit information of NCI sponsored sites is confidential, therefore they will not provide this information to Genentech for inclusion in the resubmission. However, NCI will work with the FDA to provide pertinent summary information. NCI needs guidance on details of the summary. FDA noted that when a company conducts a trial, all protocol deviations that occurred at a particular site are noted and described in detail in an application or supplement. The data is presented such that for any unacceptable findings, FDA is able to relate an investigator to the patient ID number. The current NCI audit system does not allow the FDA to do so. NCI should provide a list of investigator/investigational sites who participated in E2100 study who had unacceptable audit findings and a listing of the specific deficiencies identified during the audit.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

1. Submission of survival data. Need agreement on cut-off date.
2. Submission of clinical study site audit reports

ACTION ITEMS:

1. Genentech will submit the IRF charter and modified RECIST criteria.
2. Genentech will submit a revised SAP.

APPENDIX: Timeline of Events

APPENDIX: Timeline of Events

- October 18, 2001** NCI submits E2100 protocol to IND 7921.
- November 14, 2001** NCI submits to IND 7921 a revised protocol incorporating the September 18, 2001 changes to the protocol required by NCI's Central IRB.
- November 2001** On-going Phase 3 Genentech AVF 2119g trial completes accrual.
- November 20, 2001** In a teleconference, FDA asked Genentech to provide clarification of their overall Bevacizumab development strategy focusing on the identification of registration trials and proposed timelines.
- March 14, 2002** Genentech responds to November 20, 2001, FDA request and identifies E2100 and _____ b(4)
- May 2, 2002** Beginning on this date, FDA communicates to NCI in a series of letters their concern regarding E2100 protocol design and data collection.
- September 9, 2002** Genentech releases *negative* results of AVF 2119g breast cancer trial.
- April 14, 2005** ECOG does initial analysis of E2100 data and partially releases information.
- May 2005** E2100 data presented at American Society of Clinical Oncology annual meeting.
- August 25, 2005** Genentech submits efficacy results from E2100 to IND 7023 as part of the meeting package for the pre-sBLA meeting in September 2005.
- September 28, 2005** Pre-sBLA meeting with FDA, Genentech and NCI.
- May 23, 2006** Genentech submits a sBLA for Avastin first line breast cancer in combination with docetaxel supported by a single pivotal study (E2100).
- July 21, 2006** FDA issues letter to Genentech filing the sBLA and noting the deficiencies.
- September 8, 2006** FDA issues Complete Response letter to Genentech.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125985/91

FEB 12 2007

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

Dear Dr. Rich:

This letter is in regard to the supplement to your biologics license application for Bevacizumab submitted under Section 351 of the Public Health Service Act.

We have reviewed your November 13, 2006, submission containing an Independent Review Facility (IRF) Charter which will be used to reassess progression free survival and response rate in all 722 patients on study E2100.

We have the following comments and recommendations for revision of the charter:

1. As proposed by Genentech during the November 2, 2006, Type A meeting, an independent review to validate the primary endpoint of PFS will be conducted in all 722 patients enrolled in the E2100 study. Please revise the IRF Charter accordingly.
2. Please revise the charter to include provisions for qualification standards and training for quality assurance of the selected independent radiology readers. Please submit a copy of the training manual, if any, which will be provided to the independent radiology reviewers.
3. Please pre-specify the provisions for handling all potential missing data as related to missing time points, data validation, technically inadequate quality images, proposed modifications, and justifications.

We have identified the following concerns, which although they may not be subject to remedy, will impact the reliability of the study results:

4. The difficulty in performing a retrospective (post-hoc) review of images performed without pre-specified imaging requirements or protocol. Assessment of objective time point response comparison measurements utilizing the modified RECIST criteria is potentially further confounded by:
 - a. Changes in imaging modalities or technical parameters of scans.

- b. Use or lack of use of oral contrast agents for each imaging study.
 - c. Use or lack of use of intravenous contrast agents for each imaging study.
 - d. Lack of uniformity in image acquisition due to variations in individual radiology facility's imaging protocols.
5. The lack of standardization, the lack of pre-specified uniformity in the methods of collection of radiological and clinical data at pre-specified time points, and the lack of uniform availability of data for all subjects to all radiological and oncological reviewers.
6. Utilization of the radiologist assessment as the final assessment for subjects without medical information pertinent to an oncology review (when the oncologist confirms the absence of medical information).

If you have any questions, please contact Ms. Sharon Sickafuse, Regulatory Project Manager, at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125085/91

FEB 12 2007

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

Dear Dr. Rich:

This letter is in regard to the supplement to your biologics license application for Bevacizumab submitted under Section 351 of the Public Health Service Act.

We have reviewed your January 9, 2007, submission which contained a revised statistical analysis plan (SAP) for study E2100.

We have the following comments:

1. The SAP states that the overall survival (OS) analysis will be based on all information available at the time of the final data transfer per communication with the Agency following the November 2, 2006, meeting.

You must provide a cut-off date for the interim OS data to be included in the sBLA resubmission. We recommend that the data include information present in the ECOG database shortly before the planned date of the resubmission.

Please note that an agreement regarding the OS data submission was not reached during the informal electronic communication between Dr. Lisa Bell and Dr. Patricia Keegan.

2. Please propose imputation methods for missing data to assess the robustness of the Quality of Life (QoL) results. QoL analyses should be exploratory if there is a substantial amount of missing data.

If you have any questions, please contact Ms. Sharon Sickafuse, Regulatory Project Manager, at (301) 796-2320.

Sincerely,



Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BLA STN 125085/91

DEC 12 2006

Genentech, Incorporated
Attention: Todd Rich, M.D.
Vice President, Clinical and Commercial Regulatory Affairs
1 DNA Way MS #232
South San Francisco, CA 94080

Dear Dr. Rich:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Bevacizumab.

We also refer to the November 2, 2006, meeting between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

A handwritten signature in black ink that reads "Sharon Sickafuse".

Sharon Sickafuse, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 2, 2006
APPLICATION: STN 125085/91
SPONSOR: Genentech, Incorporated
DRUG NAME: Bevacizumab
INDICATION: First-line treatment of locally recurrent or metastatic breast cancer
TYPE OF MEETING: Type A

MEETING RECORDER: Sharon Sickafuse

FDA ATTENDEES:

Office of Oncology Drug Products

Richard Pazdur, M.D.

Karen Weiss, M.D.

Division of Biologic Oncology Products

Joe Gootenberg, M.D.

Karen Jones

Patricia Keegan, M.D.

Steven Lemery, M.D.

Lee Pai-Scherf, M.D.

Kaushik Shastri, M.D.

Sharon Sickafuse, M.S.

Jeff Summers, M.D.

Office of Biostatistics

Division V

Laura Lu, Ph.D.

Mark Rothmann, Ph.D.

Office of the Commissioner

Office of Special Health Issues

Patricia Delaney

Blair Schwartz

Erin Robey

Melissa Vogel

SPONSOR ATTENDEES:

Genentech, Inc.

Alex Bajamonde, Ph.D., Director of Biostatistics
Lisa Bell, Ph.D., Associate Director, Regulatory Affairs
Gwen Fyfe, M.D., Vice President, BioOncology
Barbara Klencke, M.D., Senior Medical Director, BioOncology
Chandra Lovejoy, Manager, Regulatory Affairs
Bob Mass, M.D. Principal Medical Director, BioOncology
Michael Ostland, Ph.D., Associate Director, Biostatistics
Todd Rich, M.D., Vice President, Regulatory Affairs
David Schenkein,
Xiaolin Wang, Sc.D., Associate Director, Biostatistics
Kathie Winson,
Beiyao Zheng, Ph.D., Senior Statistical Scientist, Biostatistics

NCI/CTEP:

Jeff Abrams, M.D., Associate Chief – Medicine, Clinical Investigations Branch
Helen Chen, M.D., Senior Investigator, Investigational Drug Branch
Michaele Christian, M.D., Associate Director
Sally Hunsberger,
JoAnne Zujewski, M.D., Senior Investigator, Breast Cancer Therapeutics, Clinical Investigations Branch

Eastern Cooperative Oncology Group (ECOG):

Robert Comis, M.D., Group Chair
Robert Gray, Ph.D., Group Statistician
Deidre Levine,
Donna Maranucci,
Kathy Miller,
Mary Steele,

BACKGROUND: The NCI submitted study E2100, "A Randomized, Phase 3 Trial of Paclitaxel Versus Paclitaxel Plus Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer" to IND 7921 on October 18, 2001. The protocol was submitted to the FDA before the NCI Central IRB's September 18, 2001, required revisions were incorporated. Those revisions were subsequently made and a revised protocol was submitted to IND 7921 on November 14, 2001.

The protocol background information in the November 14, 2001 submission described prior experience with Bevacizumab in Study AVF0776g, "An Open-label, Dose-ranging, Phase 2 Study of Single Agent Avastin Conducted in Women Receiving Second-line Treatment for Metastatic Breast Cancer." The background section contained no references to Genentech's AVF2119g Phase 3 study of Bevacizumab in breast cancer. Study AVF2119g completed accrual in November 2001 and negative results were released on September 9, 2002.

During the November 20, 2001, teleconference requested by Genentech to discuss the results of a Phase 2 trial conducted by NCI to support labeling expansion for another indication (not breast cancer), FDA requested that Genentech provide clarification of their overall Bevacizumab development strategy and the role of NCI trials in that development strategy. Genentech agreed to provide a compendium of ongoing trials and an updated Bevacizumab development plan focusing on registration trials and proposed timelines. Genentech submitted their response to FDA's request to IND 7023 on March 14, 2002, identifying E2100 and two additional trials being conducted under NCI's IND 7921 as "non-Genentech trials intended to support a possible license application." Subsequent to receipt of this information, FDA communicated concerns to NCI regarding the protocol design and data collection for study E2100 in a series of letters, beginning on May 2, 2002.

The results of E2100 were analyzed by ECOG, with initial public release on April 14, 2005, presented at the May 2005 ASCO meeting, and submitted as an amendment to Genentech's IND 7023 on August 25, 2005, as part of the meeting package for the pre-sBLA meeting held September 28, 2005. During the pre-sBLA meeting, Genentech posed the following question:

".... Genentech believes that the highly significant PFS results, a trend in overall survival, and the safety profile observed with Bevacizumab in Study E2100 are sufficient to support an sBLA to extend the current indication of Avastin to the following: _____

_____.' Does the Agency agree that this study can form the basis for this sBLA?"

b(4)

The efficacy results provided in the August 25, 2005, submission included an improvement in overall response rate (14.2% vs. 28.2%, $p < 0.0001$) and an encouraging comparison in overall survival (HR=0.674, log-rank test, $p = 0.01$).

The importance of the results on overall survival to the review of this application were further clarified in FDA's response to the following question, posed by Genentech during the September 28, 2005 meeting:

"Given the strength of the PFS data and the known safety profile of Bevacizumab, does the Agency agree that: ...The data will support full approval?"

FDA's response provided to Genentech prior to the September 28, 2005, meeting stated: "No. The endpoint of PFS will support an accelerated approval. At the time of filing, please submit data on overall survival. Mature data concerning overall survival will be requested as a post-marketing commitment and will convert the sBLA from accelerated approval to full approval."

The meeting minutes generated by FDA captured the following additional discussion: "Genentech noted that cross-over was not allowed in study E2100. Since the public release of information concerning E2100, ECOG has not noted an increase in the number of patients in the control arm who discontinue paclitaxel (with or without progression) and then initiate chemotherapy plus commercially available Bevacizumab."

On May 23, 2006, Genentech submitted a sBLA for study E2100. In contrast to the "trend in overall survival" described at the September 28, 2005, meeting, the updated survival information contained in the efficacy supplement showed an erosion of the effect and raised concern about the effect on overall survival suggested by the earlier analyses (HR=0.821, p=0.082 stratified log-rank). FDA issued a letter on July 21, 2006, filing the supplement and identifying deficiencies. On September 8, 2006, FDA issued a complete response (CR) letter.

On September 29, 2006, Genentech submitted a request for a type A meeting to discuss the September 8, 2006, CR letter. The meeting package was submitted on October 18, 2006. Draft FDA responses to Genentech's questions were provided to Genentech on November 1, 2006.

MEETING OBJECTIVES: Discuss how Genentech can best address the September 8, 2006, CR letter and how to ensure that the content of their response addresses the most important review issues.

Genentech opened the meeting with the following new proposals (not described in the meeting package):

New Safety Data Proposal:

Rather than provide all safety data (including MedWatch and AdEERS forms) identified as occurring on or before the data cut-off date of February 9, 2005, as stated in the meeting package, Genentech now proposed to include all safety data through August 2005. Genentech justified this proposal based on the following information:

As of August 2005, only 42 patients were still receiving treatment (35 on the Bevacizumab arm and 7 on the control arm). Ninety-four percent of all patients registered and randomized have completed all protocol treatment and safety data collection (excluding survival information). Genentech stated that 7 additional AdEERS reports have been generated for events occurring after August 9, 2005.

FDA expressed concerns with this proposal particularly for AdEERS reporting, given that measurable levels of Bevacizumab are present for at least 6 months after the last dose. FDA expressed a preference for a later cut-off date for serious adverse events (AdEERS/MedWatch reports); Genentech proposed and FDA agreed that inclusion of all AdEERS reports through October 7, 2006, was acceptable. In addition, FDA stated that February 9, 2005, would not be an acceptable cut-off date for survival data.

This issue of the data cut-off date for survival information remains outstanding.

Progression Free Survival (PFS) Endpoint Validation Proposal:

In response to FDA's draft responses provided to Genentech on November 1, 2006, Genentech stated at the meeting that they will perform an independent review to validate the primary endpoint of PFS in all 722 patients using the modified RECIST criteria. The independent review facility (IRF) will receive all imaging scans as well as pertinent clinical data. Genentech will

perform due diligence to collect scans on all 722 patients and anticipates that they will have collected more than 90% of the scans by the end of March 2007.

FDA stated that Genentech's proposal for an independent review of all patient films, with PFS determined using the modified RECIST criteria was acceptable. Genentech will submit the IRF charter to FDA for review and comment.

Genentech stated that they will make the following revisions to the statistical analysis plan (SAP) which will be submitted to FDA:

- The primary analysis is based on IRF data.

FDA agreed with this revision.

- The definition of PFS will be amended to not include deaths that occurred greater than _____ after the last treatment.

b(4)

FDA recommended that the definition of PFS be amended to censor at the date of the last study visit those patients whose deaths occurred more than 84 days after the last treatment. Genentech agreed to do this.

Genentech proposed not to include images in the sBLA resubmission, however films would be available upon request. FDA agreed with this proposal.

SPONSOR QUESTIONS AND FDA RESPONSES:

1. *Genentech believes that endpoint validation is a central issue of our recent complete response letter. What data should be included in this submission to ensure that the Agency can assess the adequacy of this trial for approval?*

FDA Response:

Endpoint validation is one of the many issues of the CR letter. The lack of a locked data set with ongoing data collection and clean up made it impossible for the FDA to assess the conduct of the study and the efficacy and safety of your claim.

Justification of the sample size for endpoint validation must be based on the projected number, direction, and magnitude of the discordant readings between the investigator and the masked, external review for outcomes.

Discussion: See Progression Free Survival (PFS) Endpoint Validation Proposal above. FDA agreed that a re-analysis of PFS by an independent review committee that included more than 90% of the patients was acceptable.

2. *Genentech would like to request specific guidance as to what would enable inclusion of the progression-free survival (PFS) hazard ratio and medians and objective response rate in the label?*

FDA Response:

Genentech must provide data that demonstrates that the investigator assessed response is reliable based on an independent endpoint validation and the April 5, 2005, SAP which FDA has indicated is acceptable. FDA is willing to discuss this issue further pending submission of the IRF findings.

Discussion: See Progression Free Survival (PFS) Endpoint Validation Proposal above.

3. *Genentech proposes to include preliminary overall survival information in the label. Does the Agency agree?*

FDA Response:

We are unable to comment on the label at this time. However, inclusion of an unplanned analysis is unlikely. All analyses must be consistent with the accepted pre-specified SAP of April 4, 2005.

Discussion: Genentech stated that the final analysis of survival is not expected to occur until November 2007. The final overall survival analysis will be completed when there are 481 events. The SAP did not provide any plans for interim analyses of survival. For the purposes of safety, not for demonstrating efficacy, FDA requested that an unplanned interim analysis of survival be provided in the resubmission. The cut-off date for this interim analysis was not agreed upon at the meeting, however FDA stated that this information is important in characterizing safety and is critical to the review of the resubmission. FDA stated and Genentech acknowledged that formal comparison from an unplanned interim analysis of survival cannot be included in product labeling.

4. *To ensure that the intent of the complete response letter is met, Genentech requests that the Agency clarify whether there are any other review issues involving new data that Genentech should consider in working with ECOG on the resubmission.*

FDA Response:

Additional review issues might arise during the review of your resubmission.

Discussion: FDA clarified that it has no additional concerns that were not already stated in the September 8, 2006, CR letter, however new issues may arise as a result of the new information to be provided in the resubmission.

5. *Does the Agency agree with Genentech's proposal for the content and format of the sBLA resubmission of the clinical study report, patient narratives, case report forms (CRFs), and case report tabulations?*

FDA Response:

Yes. The overall content is acceptable.

Discussion: None.

6. *Does the Agency agree with the methodology used for applying the cutoff date of February 9, 2005?*

FDA Response:

The cut-off date of February 9, 2005, is acceptable for the primary efficacy analysis. However, for safety and survival, the cut-off date should be no earlier than October 2006. The data that has been submitted in accordance with the ECOG-specified timeframes for data reporting should be provided. We note that more than 2 years will have elapsed since the February 2005 cut-off and the proposed resubmission.

Discussion: FDA restated that a cut-off date of February 2005 for tumor assessments (PFS) is acceptable. Genentech noted that the original submission contained all survival data received as of December 2005 and proposed to provide data on all deaths occurring on or before February 2005. FDA did not agree with Genentech's proposal and stated that all survival data through October 2006 (cleaned) or through March 2007 (data submitted, but not verified to be 100% complete or accurate) must be provided. NCI and ECOG argued that collection of interim survival information is time consuming and would require strenuous resources that are unnecessary for the sBLA resubmission. FDA strongly disagreed, noting that the request would be based on data captured on a single CRF and restricted to the single element of survival status. Although interim analysis of survival data was not pre-specified in the analysis plan for efficacy, FDA strongly recommended that Genentech provide up-to-date survival information at the time of sBLA resubmission as part of the safety analysis. FDA will not review and will not approve an efficacy supplement based on survival information that lacks data collected over a 2-year period.

Regarding the cut-off date for safety, see the New Safety Data Proposal above.

7. *Genentech proposes to submit a _____ that would include new events reported during the period between _____. Does the Agency agree with the proposal for the _____ as described?*

b(4)

FDA Response:

No. Please refer to our answer to your question #6 above.

Discussion: FDA agreed that because all serious adverse events through October 2006 will be provided in the resubmission and all other adverse events through August 2005 were provided in the original submission, a _____ need not be submitted during the resubmission review period.

b(4)

Regarding Comment 1 in the September 8, 2006, CR letter:

8. *Is the data cutoff date of 9 February 2005 for the resubmission acceptable to the Agency?*

FDA Response:

No. Please refer to our answer to your question #6 above.

Discussion: This was addressed in response to previous comments/questions.

Regarding Comment 2 in the September 8, 2006, CR letter:

9. *Does the Agency agree with Genentech's proposal to conduct the IRF review using a charter based on the modified Response Evaluation Criteria in Solid Tumors (RECIST)?*

FDA Response:

No. As discussed during the teleconference of August 2, 2006, and in our email to your of August 30, 2006, the IRF review must be conducted using the same criteria as the investigator was required to use during the conduct of the study. The IRF review can use Genentech's proposed modified criteria if the review is conducted in all 722 patients enrolled in the study.

Discussion: This was addressed in response to previous comments/questions. See Progression Free Survival (PFS) Endpoint Validation Proposal above.

10. *Can the Agency provide further specific guidance as to the evidence required to warrant inclusion of the PFS hazard ratio and point estimate for the medians as well as the response rates in the label?*

FDA Response:

Please refer to our answer to your question #2 above.

Discussion: This was addressed in response to previous comments/questions.

11. *Genentech believes that endpoint validation is a central issue of our recent complete response letter. What data should be included in the submission to ensure that the Agency can assess the adequacy of this trial for approval? In particular, Genentech requests clarification from the Agency as to whether the confidence interval approach is*

appropriate for sample size justification. In addition, Genentech requests feedback from the Agency as to the sample size sufficient for endpoint verification.

FDA Response:

Please refer to our answer to your question #1 above.

Discussion: This was addressed in response to previous comments/questions.

Regarding Comment 3 in the September 8, 2006, CR letter:

12. *Does the Agency with Genentech's proposal to submit the eligibility checklist information? If so, does the Agency agree with Genentech's proposal to provide eligibility checklists and CFRs for all 722 patients enrolled in Study E2100?*

FDA Response:

Yes. Queries, corrections and their explanations must be provided via hyperlink in the CRF.

Discussion: ECOG clarified that the eligibility checklist form from the investigational sites is a working form and is not always accurate or complete. ECOG's internal forms are more accurate, however ECOG's review does not include an assessment of all factors required to verify eligibility (e.g., review of laboratory values). ECOG will work with Genentech to provide eligibility checklists on all 722 patients which will be converted to pdf files and provided in the resubmission. This is acceptable to the FDA.

Regarding Comment 4 in the September 8, 2006, CR letter:

13. *Does the Agency agree with Genentech's proposal for providing dataset, ECOG Eligibility Evaluation Forms, and ECOG Case Evaluation Forms?*

FDA Response:

Yes.

Discussion: None.

Regarding Comment 5 in the September 8, 2006, CR letter:

14. *Does the Agency agree with Genentech's proposal to submit objective response information for all randomized patients with measurable and non-measurable disease?*

FDA Response:

Yes.

Discussion: None.

Regarding Comment 6 in the September 8, 2006, CR letter:

15. *Does the Agency agree with Genentech that it is not possible to quantify the extent of involvement for each non-target lesion?*

FDA Response:

Please note that comment #6 of the CR letter refers to non-measurable disease and not non-target lesions.

In addition to reporting the site of involvement for each non-measurable lesion, all descriptive information and verbatim information should be included in the resubmission.

Discussion: Genentech did not request clarification. Genentech will provide the data requested by FDA in the resubmission as follows: identification in the datasets of the site of the non-measurable lesion, the method used to characterize tumor response/progression, and the date of assessment. FDA requested, and Genentech agreed to provide, descriptive information regarding any assessment of disease progression/response at the non-measurable lesion site in a comment field.

16. *Does the Agency wish Genentech to instead report the site of involvement for each non-target lesion?*

FDA Response:

Please see comment #15 above.

Discussion: None.

17. *Does the Agency agree with Genentech's proposal for providing a listing for patients with non-measurable disease at baseline?*

FDA Response:

Yes.

Discussion: None.

Regarding Comment 7 in the September 8, 2006, CR letter:

18. *Genentech requests that the Agency confirm the acceptability of our response to collect no new data.*

FDA Response:

Yes, however failure to fully characterize some aspects of drug therapy may result in limitations in product labeling.

Discussion: Genentech expressed understand of the possible consequences of missing data.

Regarding Comment 8 in the September 8, 2006, CR letter:

19. *For the analysis of objective response, does the Agency agree with Genentech's proposal that the primary analysis population consist of patients with measurable disease at baseline, with a supporting analysis including all randomized patients?*

FDA Response:

Yes.

Discussion: None.

Regarding Comment 9 in the September 8, 2006, CR letter:

20. *Does the Agency agree with Genentech's proposal to provide information necessary to determine how patients with unevaluable or unknown response status were evaluated regarding PFS?*

FDA Response:

Yes. All descriptive, verbatim information should be included.

Discussion: None

Regarding Comment 10 in the September 8, 2006, CR letter:

21. *Does the Agency agree with Genentech's proposal to provide a summary of missing response assessments per timepoint as specified in the E2100 SAP of April 5, 2005?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 11 in the September 8, 2006, CR letter:

22. *Does the Agency agree with Genentech's proposal to provide comprehensive efficacy results for the interim analysis based on the February 9, 2005, database cut-off?*

FDA Response

Yes. It is FDA's understanding that this dataset and the analysis of disease-free survival will include all events occurring on or before February 9, 2005, and that all patients lost to follow-up prior to February 9, 2005, will be flagged. Genentech must also provide updated safety and survival data at the time of resubmission. Your proposal for censoring for overall survival is not acceptable. Patients who died past February 9, 2005, should be censored on this date, not the date of last follow-up.

Discussion: Genentech agreed to censor patients who died past February 9, 2005, on this date, not the date of last follow-up.

Regarding Comment 12 in the September 8, 2006, CR letter:

23. *Does the Agency agree with Genentech's proposal to provide a dataset as of the February 9, 2005, cut-off date that includes all of the variables in the current PATE.xpt dataset?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 13 in the September 8, 2006, CR letter:

24. *Does the Agency agree with Genentech's proposal not to include these SAS programs in our upcoming resubmission?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 14 in the September 8, 2006, CR letter:

25. *Does the Agency agree with Genentech's proposal to address the Agency's requests as presented in our response to item 14a of the September 8, 2006, complete response letter?*

FDA Response:

Given that height, weight, or BSA information were not collected by study sites, the proposed retrospective assumptions are acceptable.

Discussion: None

26. *Genentech requests that the Agency confirm that _____ is acceptable as the reason provided for a dose modification or omission.*

FDA Response:

Please provide the analysis and the dataset analysis program of adverse events occurring prior to or during any treatment cycle in which a _____ dose modification occurred.

Discussion: Genentech agreed to provide this information.

27. *Does the Agency agree with Genentech's proposal to provide a listing and tabulation for patients in the paclitaxel + Bevacizumab arm that include whether the dose modification or omission was planned or unplanned for each 3-cycle reporting period for each treatment arm?*

FDA Response:

Yes; however you should also provide additional analyses as described above in item #26.

Discussion: Genentech agreed to provide this information.

28. *Does the Agency agree with Genentech's proposal to address the Agency's requests as presented in our response to items 14c-14h of the September 8, 2006, complete response letter?*

FDA Response:

Yes.

Discussion: None

b(4)

29. *Does the Agency agree with the proposed format and content for the narratives?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 15 in the September 8, 2006, CR letter:

30. *Does the Agency agree with Genentech's proposal to provide financial disclosure information for the Lead Principal Investigators for Study E2100?*

FDA Response:

Yes.

Discussion: None

Regarding Comment 17 in the September 8, 2006, CR letter:

31. *Does the Agency agree with Genentech's proposal to provide _____?*

b(4)

FDA Response:

No. For each study site audited during the conduct of E2100, please provide a summary evaluation of the audit results. For sites with unacceptable findings, provide justification for inclusion of study data.

Discussion: NCI stated that full audit information of NCI sponsored sites is confidential, therefore they will not provide this information to Genentech for inclusion in the resubmission. However, NCI will work with the FDA to provide pertinent summary information. NCI needs guidance on details of the summary. FDA noted that when a company conducts a trial, all protocol deviations that occurred at a particular site are noted and described in detail in an application or supplement. The data is presented such that for any unacceptable findings, FDA is able to relate an investigator to the patient ID number. The current NCI audit system does not allow the FDA to do so. NCI should provide a list of investigator/investigational sites who participated in E2100 study who had unacceptable audit findings and a listing of the specific deficiencies identified during the audit.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

1. Submission of survival data. Need agreement on cut-off date.

2. Submission of clinical study site audit reports

ACTION ITEMS:

1. Genentech will submit the IRF charter and modified RECIST criteria.
2. Genentech will submit a revised SAP.

APPENDIX: Timeline of Events

APPENDIX: Timeline of Events

- October 18, 2001** NCI submits E2100 protocol to IND 7921.
- November 14, 2001** NCI submits to IND 7921 a revised protocol incorporating the September 18, 2001 changes to the protocol required by NCI's Central IRB.
- November 2001** On-going Phase 3 Genentech AVF 2119g trial completes accrual.
- November 20, 2001** In a teleconference, FDA asked Genentech to provide clarification of their overall Bevacizumab development strategy focusing on the identification of registration trials and proposed timelines.
- March 14, 2002** Genentech responds to November 20, 2001, FDA request and identifies E2100 and _____ b(4)
- May 2, 2002** Beginning on this date, FDA communicates to NCI in a series of letters their concern regarding E2100 protocol design and data collection.
- September 9, 2002** Genentech releases *negative* results of AVF 2119g breast cancer trial.
- April 14, 2005** ECOG does initial analysis of E2100 data and partially releases information.
- May 2005** E2100 data presented at American Society of Clinical Oncology annual meeting.
- August 25, 2005** Genentech submits efficacy results from E2100 to IND 7023 as part of the meeting package for the pre-sBLA meeting in September 2005.
- September 28, 2005** Pre-sBLA meeting with FDA, Genentech and NCI.
- May 23, 2006** Genentech submits a sBLA for Avastin first line breast cancer in combination with docetaxel supported by a single pivotal study (E2100).
- July 21, 2006** FDA issues letter to Genentech filing the sBLA and noting the deficiencies.
- September 8, 2006** FDA issues Complete Response letter to Genentech.

Jones, Karen

From: Lisa Bell [bell.lisa@gene.com]
Sent: Friday, September 08, 2006 5:23 PM
To: Jones, Karen
Cc: Sickafuse, Sharon
Subject: RE: sBLA 125085/91 Letter
Attachments: emfalert.txt

Got it. Thanks!

From: Jones, Karen [mailto:karen.jones@fda.hhs.gov]
Sent: Friday, September 08, 2006 2:19 PM
To: Lisa Bell
Cc: Sickafuse, Sharon
Subject: sBLA 125085/91 Letter
Importance: High

Hello Lisa,

Sharon Sickafuse has informed me that you prefer to receive the CR letter we are issuing to you today for STN BL 125085/91 via email. The letter is attached. Please send confirmation of receipt via email to Sharon Sickafuse and cc me.

-20060908171007.pdf>>

Thank you very much.

Karen D. Jones
Chief, Project Management Staff
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
301-796-1377; fax 301-796-9849

Sickafuse, Sharon

From: Jones, Karen
Sent: Wednesday, August 30, 2006 5:30 PM
To: 'Lisa Bell'
Cc: Sickafuse, Sharon; Pai-Scherf, Lee
Subject: RE: IRF charter review

STN 125085/91

hello Lisa,

We have reviewed the E2100 IRC Charter and we have the following comments.

1. The IR Review Procedures Document states that all images will be reviewed and response assessed using modified RECIST (appendix A). This is a retrospective analysis to confirm ECOG response and PFS findings, hence we recommend that characterization of disease sites, response criteria, definition of measurable and non-measurable disease follow the same criteria as specified in the E2100 protocol, used by the ECOG investigators i.e., RECIST (Tharasse, 2000).

Please revise the Independent Radiology Review Procedures Document accordingly.

2. Please provide detailed information as to how patients with non-measurable disease will be handled by the IRC team.

Thank you.

Karen Jones, CPMS

OODP/DBOP

From: Lisa Bell [mailto:bell.lisa@gene.com]
Sent: Tuesday, August 29, 2006 2:15 PM
To: Jones, Karen
Subject: IRF charter review

Karen,
I was wondering if you knew who had been assigned to the review of the charter for supplement 91. We had asked whether it might be possible to have the same person who reviewed the IRF charter for supplement 85 look at this one. Since it's a different division I understand that's out of your hands but we're also trying to figure out what the likelihood is that we might receive significant comments on the charter (the last reviewer only had minor edits). In particular comments regarding the radiology review, which was most identical between the two documents, would have an impact to our timelines. Don't mean to be a pain it's just that this will help with our planning.
Thanks in advance for your assistance.
sa

Lisa Bell, Ph.D.
Associate Director, Regulatory Affairs
Genentech, Inc.

4S 242

Way
San Francisco, CA 94080
h: 650-225-3512
AX: 650-225-1397

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Tuesday, August 01, 2006 3:51 PM
To: 'Chandra Lovejoy'
Subject: STN 125085/91 - FDA response to questions re draft charter

Importance: High

Attachments: 2100SummaryIRFcharter.FDAcomments.doc



2100SummaryIRFcharter.FDAcomments.doc

Dr. Pai-Scherf's response is attached.

-----Original Message-----

From: Chandra Lovejoy [mailto:lovejoy.chandra@gene.com]
Sent: Friday, July 28, 2006 5:01 PM
To: Pai-Scherf, Lee
Cc: Jones, Karen; Conner, Beverly; 'Lisa Bell'
Subject: RE: E2100 sBLA: Request for clarification (FDA fax received July 21)

Hi Lee,

I have attached a summary of the IRF charter for supplement 91. If possible, please let me know by next Wednesday if you have any concerns. Thank you in advance for your time and thoughts.

Kind Regards,
Chandra

FDA comments regarding the summary of the IRF charter for supplement 91 (received July 28, 2006):

1. The definition of progressive disease as outlined in the summary of IRF methodology differs from the RECIST criteria and as outlined in the clinical protocol (section 16.1.15, page 1228 of e2100 CSR). PD should be defined as a \geq 20% increase in SLD of target lesions taking as reference the smallest sum longest diameter recorded during the study, or the appearance of one or more new lesions. Please revise accordingly.
2. Please provide a detailed plan for handling of missing data (films and/or clinical assessment).
3. IRF source document provided to the FDA should contain individual patient's listing of target and non-target lesions, serial tumor measurements and assessment by individual readers. Clinical data (source document) to support the final assessment by the oncologist must be provided for each patient.
4. A report authored by Genentech describing the findings of the independent efficacy review is acceptable. Please also submit the final report by the IRF.

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

Memorandum

Telecon July 28, 2006

Date:

From: Karen D. Jones, CPMS
FDA/CDER/OND/OODP/DBOP

Subject: Genentech Inc.'s Bevacizumab (Avastin) sBLA 125085/91

FDA Participants:

Patricia Keegan, M.D., Division Director OODP/DBOP
Kaushikkumar Shastri, M.D., Medical Team Leader, OODP/DBOP
Lee Pai-Scherf, M.D., Medical Officer, OODP/DBOP
Karen D. Jones, CPMS, OODP/DBOP
Beverly Conner, RPM, OODP/DBOP
Laura Lu, Ph.D., Biostatistician, OB, DB V

Sponsor Attendees:

Lisa Bell
Alex Bajamonde
Julie Hambleton
Bei-yao Zheng
Howard Mackey
Bob Mass

Telecon Purpose: To discuss the Genentech proposal for the Avastin study E2100 safety update.

Discussion:

1. FDA opened discussion by asking Genentech if the planned safety update for the Avastin E2100 study includes the SAEs and AEs that occurred after the study data cut-off time point of 12/31/05 or does it include newly identified patients with adverse events that occurred prior to 12/31/05? FDA stated that, as of December 30, 2005, only 11 patients remained on the paclitaxel arm and 38 patients remained on the paclitaxel + Avastin arm, thus the numbers of AEs and SAEs to be updated should be low. FDA would like to know if the new data will result in changed incidence figures in the package insert label.
 - Genentech stated that the safety update, as currently planned, will include approximately 30-35 new death events and 11 new SAEs. It is expected that very few

of these events occurred prior to 2005. The safety update will also include newly identified patients requiring narratives, updated safety and exposure datasets. These changes are likely to require revision of the draft package insert already submitted in the supplement.

2. FDA stated that the agency would like an independent audit of a proportion of the efficacy data to verify "softer" endpoints (PFS with no benefit of survival). All of the information should be submitted as a single submission.
 - Genentech expressed concern that the review is stopping until the new submission is received and inquired about the impact on the PDUFA goal date.
 - FDA agreed that the PDUFA goal would be impacted as the new submission will be considered a major amendment to the supplement.
3. FDA also indicated that the important topic of verification of data for "softer endpoints" (in this case, PFS with no benefit of survival) would likely be brought before an advisory committee, however, FDA would like to see the major amendment prior to making a decision. The expectation would be to go before the ODAC in the late January-early February time frame.
 - Genentech expressed willingness to work with FDA, but noted that they had not planned on updating progression; 27 patients are still on therapy, 2 on the control arm. Genentech is concerned about not being able to provide updated safety, survival and PFS information until early November with an action goal date of late November
 - FDA responded that the Agency is asking for verification of the data submitted and confirmation that it includes all events as of the purported cut-off. If the Agency had been aware that there was no survival benefit, the Agency would have advised Genentech differently and at an early point in the discussions of application content. If ongoing data clean-up affects the efficacy endpoints of PFS and response rates/durations, FDA will need to see the more accurate data. The FDA's expectation was that the database would have been "cleaned up" prior to submission of the data such that all data errors and discrepancies would have been identified and resolved.

Agreements/Action Items:

- Genentech will submit a new dataset that includes radiologic review in the fall of 2006. This submission will likely be a major amendment.
- The submission will likely be brought before ODAC in early 2007.
- Genentech will submit a draft IRF charter to Dr. Pai-Scherf for review prior to initiation of the external radiologic review. Genentech requested that the same Office of Oncology Division of Medical Imaging and Hematologic Products (DMIHP) consult reviewer who reviewed the Avastin NSCLC draft IRF charter also review the IRF charter for this breast cancer supplement. FDA agreed to request the same DMIHP consult reviewer.

The teleconference concluded.



Our STN: BL 125085/91

JUL 21 2006

Genentech, Incorporated
Attention: Robert L. Garnick, Ph.D.
Senior Vice President, Regulatory Affairs, Quality and Compliance
1 DNA Way, MS #242
South San Francisco, CA 94080-4990

Dear Dr. Garnick:

This letter is in regard to your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplement dated May 23, 2006, for Bevacizumab to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your supplement today. The user fee goal date is November 23, 2006. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified the following potential review issues which were previously communicated to you via facsimile on July 7, 2006.

1. The data to determine patient eligibility and adequacy of the conduct of trial E2100 is incomplete. Eligibility assessed using the ECOG eligibility form is available in only 605/722 patients (84%). ECOG case evaluation to determine protocol violation/deviation is available in only 261/722 patients (36%). This information is insufficient to determine if the trial supporting licensure was well conducted. Please provide eligibility and case evaluation data for all 722 patients enrolled in the study.
2. The key efficacy endpoints of Progression Free Survival (PFS) and Objective Response Rate (ORR) analyses used to support this sBLA were based on Genentech's review of ECOG's central review of investigator-reported tumor data from trial E2100. Tumor data used by ECOG and Genentech consists solely of the investigator-reported tumor lesion measurements and comment fields. Given the subjective nature of the PFS endpoint, auditing to assess data integrity in a subset of the patients must be conducted. As discussed in the teleconference on July 19, 2006, between representatives of Genentech and Drs. Pai-Scherf, Keegan and Pazdur, please perform and submit the results of an external review of the PFS data in a randomly selected subset of patients (see Attachment 1). Please form an Independent Review Committee to perform a complete, blinded review of all radiographic images and pertinent medical records.

Please submit the independent review committee charter for our review prior to implementation. Depending on the results of this evaluation, a more extensive audit may be required.

3. Please provide an efficacy dataset in which the patients included in the ECOG analysis of February 2005 are identified, such that we can determine which patients were included in the ECOG analysis of February 2005 and the outcome status at that time.
4. We note that there was a substantial difference in the number of events included in the February 2005 analysis (n=260) as compared to the April 2005 analysis (n=395). Please provide an explanation for this difference.
5. To support your assertion that the increased incidence of neuropathy in the paclitaxel plus Bevacizumab arm is due to the increase in paclitaxel exposure, please provide in tabular format, the incidence of new Grade 3 and 4 sensory neuropathy events as a function of patients at risk for each treatment arm by cycle and by cumulative dose of paclitaxel and Bevacizumab.
6. For the E2100 study, please revise the definition of major protocol deviation to include:
 - a. patients who had no evidence of disease at the enrollment; and,
 - b. patients who received non-protocol treatment prior to documented disease progression.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

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

If you have any questions, please contact, Sharon Sickafuse, at (301) 796-2320.

Sincerely,

A handwritten signature in cursive script that reads "Patricia Keegan".

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Conner, Beverly

From: Pai-Scherf, Lee
Sent: Friday, July 07, 2006 11:57 AM
To: Conner, Beverly
Cc: 'Lisa Bell'
Subject: Preliminary comments re STN 125085\91

Importance: High

Beverly,

Please forward our preliminary comments to Lisa (Genentech) via e.mail.

Thanks.

Lee

Thursday, July 06, 2006

sBLA 125085\91

Clinical Review Issues:

1. The data to determine patient eligibility and adequacy of the conduct of E2100 trial is incomplete. Eligibility assessed using ECOG eligibility form is available in 605/722 patients (84%). ECOG case evaluation to determine protocol violation/deviation is available in only 261/722 patients (36%). This information is insufficient to determine if the trial supporting licensure was well conducted. Please provide eligibility and case evaluation data for all 722 patients enrolled in the study.
2. The key efficacy endpoints of PFS and objective response rate analyses to support this sBLA were based on Genentech's review of ECOG's central review of investigator-reported tumor data from E2100 study. Tumor data used by ECOG and Genentech consists solely of the investigator-reported tumor lesion measurements and comment fields. Please form an Independent Imaging Review Committee to perform a complete, blinded review of all radiographic images of patients who reported an objective response by the investigator to confirm response status and response duration. Please submit the independent review committee charter for review prior to implementation.
3. Please provide an efficacy dataset in which the patients included in the ECOG analysis of February 2005 are identified, such that FDA can determine which patients were included in the ECOG analysis of Feb. 2005 and the outcome status at that time.
4. We note that there was a substantial difference in the number of events included in the Feb. 2005 analysis (n=260) as compared to the April 2005 analysis (n=395). Please provide an explanation for this difference.
5. To support your assertion that the increased incidence of neuropathy in the paclitaxel plus bevacizumab arm is due to the increase in paclitaxel exposure, please provide in tabular format, the incidence of new grade 3 and 4 sensory neuropathy events as a function of patients at risk for each treatment arm by cycle and by cumulative dose of paclitaxel and bevacizumab.
6. For E2100 study, please revised the definition of major protocol deviation to include:
 - a. Patient had no evidence of disease at the enrollment

b. Patient received non-protocol treatment prior to documented disease progression



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

REVIEW MEMO

From: Beverly ^{BAC}Conner, Regulatory Project Manager

Date: July 6, 2006

Through: Karen Jones, ^{KJ}CPMS

Subject: Filing Memo for Bevacizumab

STN Number: 125085/91

Supplement designation: 6-month efficacy supplement

Proposed Indication: Use of Bevacizumab in combination with taxane-based chemotherapy for the treatment of patients who have not received chemotherapy for locally recurrent or metastatic breast cancer.

b(4)

Company: Genentech
License Number: 1048
Product: AVASTIN (bevacizumab)

Address:
Genentech Incorporated
1 DNA Way, MS# 242
South San Francisco, CA 94080

All Letters to:
Robert L. Garnick, Ph.D.
Senior Vice President, Regulatory Affairs,
Regulatory Affairs, Quality, and Compliance

Contact for Supplement:

Lisa M. Bell, Ph.D., Associate Director,
Regulatory Affairs
Phone Number: (650) 225-3512

Attendees:

Dr. Lee Pai-Scherf - Chairperson, Clinical Reviewer
Carole Broadnax, DDMAC Reviewer
Sharon Sickafuse, Regulatory Project Manager
Dr. Hong Lu, Statistician
Dr. Steven Lemery

Milestones:

Filing Action due Date: July 23, 2006
Deficiencies Identified Letter: August 6, 2006
First Action Date: November 22, 2006

Issues:

- DSI consult for inspection of clinical sites will not be requested since study sites overall only averaged 3.5 patients per site. Instead FDA is requesting that an External Independent Review Panel review the data.
- Genentech requesting deferral of pediatric studies, clinical reviewer agrees.
- ODAC Advisory committee is needed for supplement.
- Deficiencies were identified at the filing meeting and these issues will be communicated by letter to Genentech.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JUN 14 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 125085/91 has been assigned to your recent supplement to your biologics license application for Bevacizumab received on May 24, 2006, for use in combination with taxane-based chemotherapy for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer. **b(4)**

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,

A handwritten signature in black ink that reads "Patricia Keegan". The signature is written in a cursive style with a large initial "P".

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

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: June 6, 2006
PK 6-6-2006
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: Use in combination with taxane-based chemotherapy for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer.
To: STN 125085/91

b(4)

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: October 29, 2005
From: Sharon Sickafuse, CDER/OODP/DBOP
To: IND 7023
Subject: September 28, 2005, teleconference with Genentech regarding breast cancer study E2100

Teleconference Date: September 28, 2005

Teleconference Requestor: Genentech, Inc.

Product: Bevacizumab

Proposed Use: First line treatment of locally recurrent or metastatic breast cancer in combination with _____ **b(4)**

Teleconference Purpose: Discuss sBLA for breast cancer – study E2100 “A Randomized, Phase 3 Trial of Paclitaxel Versus Paclitaxel Plus Bevacizumab (rhUMAb VEGF) as First-line Therapy for Locally Recurrent or Metastatic Breast Cancer”.

Background: The teleconference package is amendment 594 submitted on August 25, 2005. Draft FDA responses to Genentech’s questions were faxed to them on September 28, 2005. Below are Genentech’s questions, FDA responses and the discussion that occurred during the teleconference.

Sponsor Questions and FDA Response:

1. *Genentech believes that the highly significant PFS results, a trend in overall survival, and the safety profile observed with Bevacizumab in Study E2100 are sufficient to support an sBLA to extend the current indication of Avastin to the following: “Avastin, _____” Does the Agency agree that this study can form the basis for this sBLA?* **b(4)**

FDA Response:

- An agreement cannot be reached on an indication statement prior to review of the data.
- FDA agrees that E2100 can form the basis of the primary efficacy evaluation of this sBLA.
- To provide additional safety information in patients with breast cancer, the CSRs and SAS datasets from AVF2119g and AVF0776g should also be submitted. It is not necessary to pool the datasets from these studies.

Discussion: Genentech asked whether it was necessary to submit SAS datasets for both safety and efficacy for Protocols AVF2119g and AVF0776g. FDA stated that it was only necessary to submit safety datasets along with the Clinical Study Reports for these two studies.

2. *Does the Agency agree that the ECOG DMC analysis will form the basis for assessing statistical significance of the PFS endpoint, but that the final Genentech analysis will be the primary source for the comprehensive Clinical Study Report and the label as described in Section 11.2.1?*

FDA Response: FDA noted that there was no discussion with FDA regarding the proposed design and analysis of the study prior to its initiation. Therefore, the appropriate population for the analysis of progression free survival (PFS), for purposes of labeling and promotional material, will be determined during the course of the review.

Discussion: FDA provided additional clarification with regard to reasons for not agreeing with the proposed primary analysis. FDA stated that the final version of the statistical analysis plan (SAP) was submitted on April 5, 2005, and that agreement on the acceptability of the plan had not been reached prior to the public release of information on April 14, 2005. FDA also expressed concern that the DMC analysis of PFS performed at that time used multiple cutoffs in the analysis of PFS.

3. *Does the Agency agree with the proposed changes to the Statistical Analysis Plan as described in Sections 11.2.1a and 11.2.1b?*

FDA Response:

- FDA does not object to these changes. Please submit the datasets (unless the data was not collected) necessary to perform all of the analyses included in the original SAP.

Discussion: Genentech agreed to do so.

- The pre-teleconference package states that an analysis of selected adverse events by age and race and that listings of low frequency events by age and race will be provided. Please clarify whether all adverse events will be examined by age and race. Confirm that appropriate flags will be provided in the SAS datasets to permit FDA to replicate these analyses.

Discussion: Genentech confirmed that the requested flags will be present.

- 4 *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. Genentech's proposal regarding the submission of patient narratives is acceptable, however your proposals regarding the submission of clinical study reports, case report forms, case report tabulations, and SAS datasets are not sufficient. Please include the following additional information in the sBLA:

- A clinical study report for protocol AVF0776g.
- Case report forms for all patients (in both study arms for protocol E2100) who died within 30 days of the last dose of protocol-specified treatment or discontinued treatment due to an adverse event.
- Case report tabulations for Protocols AVF2119g and AVF0776g.
- SAS datasets which include safety data from Protocols AVF2119g and AVF0776g.

Discussion: Genentech agreed to provide the requested information.

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

FDA Response: No. Genentech must provide full clinical study reports and SAS datasets for Protocols E2100, AVF2119g, and AVF0776g.

Discussion: Genentech agreed to provide full clinical study reports for protocols E2100, AVF2119g, and AVF0776g, SAS datasets (safety and efficacy) for E2100 and SAS datasets (safety only) for AVF2119g and AVF0776g.

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

FDA Response: No. Genentech must provide full clinical study reports and SAS datasets for Protocols E2100, AVF2119g, and AVF077g.

Discussion: Genentech agreed to provide full clinical study reports for protocols E2100, AVF2119g, and AVF0776g, SAS datasets (safety and efficacy) for E2100 and SAS datasets (safety only) for AVF2119g and AVF0776g.

7. *Given the strength of the PFS data and the known safety profile of Bevacizumab, does the Agency agree that:*

a. *The sBLA qualifies for priority review?*

FDA Response: Yes.

b. *The data will support full approval?*

FDA Response: No. The endpoint of PFS will support an accelerated approval. At the time of filing, please submit data on overall survival. Mature data concerning overall survival will be requested as a post-marketing commitment and will convert the sBLA from accelerated approval to full approval.

Discussion: Genentech noted that cross-over was not allowed in study E2100. Since the public release of information concerning E2100, ECOG has not noted an increase in the number of patients in the control arm who discontinue paclitaxel (with or without progression) and then initiate chemotherapy plus commercially available Bevacizumab.

FDA Attendees:

Center for Drug Evaluation and Research

Office of Oncology Drug Products

Division of Biologic Oncology Products

Patricia Keegan, M.D.

Ellen Maher, M.D.

Richard Pazdur, M.D.

Kaushik Shastri, M.D.

Sharon Sickafuse, M.S.

Office of Biostatistics

Therapeutic Biologic Statistical Staff

Mark Rothmann, Ph.D.

Sponsor Attendees:

Genentech, Inc.

Alex Bajamonde, Ph.D., Director of Biostatistics

Lisa Bell, Senior Manager, Regulatory Affairs

Barbara Klencke, M.D., Medical Director, BioOncology

Robert Mass, M.D., Group Director, BioOncology

Todd Rich, M.D.,

Michelle Roher, Ph.D., Director, Regulatory Affairs

Amy Sing, M.D., Group Director, BioOncology

Xiaolin Wang, Sc.D., Associate Director, Biostatistics

Kathy Winson, M.A., Operations Team Leader, BioOncology

Beiyao Zheng, Ph.D., Senior Statistical Scientist, Biostatistics

Eastern Cooperative Oncology Group (ECOG)

Robert Grey, Ph.D., Group Statistician

Kathy Miller, M.D., Principle Investigator

Mary Steele,

Eileen Walpole,

Molin Wang, Ph.D., Study E2100 Statistician

Cancer Therapy Evaluation Program (CTEP)

Helen Chen, M.D., Senior Investigator, Breast Cancer Therapeutics

Jo Anne Zujewski, M.D., Senior Investigator, Breast Cancer Therapeutics



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

Memorandum

Date: November 22, 2004
From: Sharon Sickafuse, CDER/ODE6/DRMP
To: IND 7023
Subject: October 28, 2004, teleconference with Genentech, NCI, and ECOG regarding the statistical analysis plan (SAP) for study E2100

Teleconference Date: October 28, 2004

Teleconference Requestor: Genentech, Incorporated

Product: Bevacizumab

Proposed Use: Treatment of recurrent or metastatic breast cancer

Teleconference Purpose: Discuss SAP for study E2100 "A Randomized Phase 3 Trial of Paclitaxel versus Paclitaxel plus Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer". See FDA letters to NCI regarding this study dated May 17, 2002, and October 24, 2002.

Sponsor Questions and FDA Response:

1. *Is study E2100 adequate in design to support a new indication for the treatment of patients with locally recurrent or metastatic breast cancer?*

Study E2100 may not be adequate to support the proposed use of Bevacizumab with paclitaxel in the treatment of patients with locally recurrent or metastatic breast cancer due to the non-blinded nature of the study and the lack of pre-specified, detailed and objective radiological and clinical parameters for determination of disease progression. FDA notes that study E2100 was not originally designed as a registration trial.

FDA does not agree with the use of the RECIST criteria in this study as the RECIST criteria were developed to determine response rates, not to determine recurrent disease.

Given the deficiencies in the study design (e.g., unblinded study and no blinded Independent Review Committee), a determination of the adequacy of the study to

support a new indication would require analysis of the study results and assessment of the conduct of the study. Furthermore, the trial, as designed, cannot be used to support accelerated approval because there is no longer an unmet medical need, due to the availability of FDA approved products for metastatic breast cancer since the initiation of the study. In support of regular approval for the proposed new indication, you must provide information regarding the effect of Bevacizumab on survival data. Finally, the results of this single study may not be sufficiently robust and thus, may need to be supported by a second positive adequate and well-controlled study in this subject population. In reviewing the results of this study, data from the previous Phase 3 study of Bevacizumab in patients with breast cancer, which failed to demonstrate efficacy, will also be considered.

2. *Does the Statistical Analysis Plan adequately address the Agency's comments provided in the letters from NCI to ECOG dated 17 May 2002 and 24 October 2002?*

With regard to your SAP, we cannot address your question until you provide clarification and additional information regarding the following aspects of the plan:

- a. Please provide the projected significance levels for your proposed interim analyses.

Genentech will provide this. They are using the O'Brian Fleming spending function which is acceptable to the FDA.

- b. The intent-to-treat population (all patients as randomized), not a subgroup of that population, should be used in the primary analysis of objective response. Patients without a post-baseline tumor assessment should be considered as non-responders and included in the analysis.

Genentech will revise the SAP such that the intent-to-treat population is used in the primary analysis of objective response.

- c. For clinical trials where the test arm involves the addition of an active therapy, the non-inferiority testing of an efficacy endpoint is not acceptable. Also, the term "non-inferior" is a misnomer and does not mean "not inferior."

Genentech will revise this. They will not be testing for non-inferiority in QOL.

- d. Time-to-treatment failure (TTF) is not an acceptable endpoint for labeling. It is a composite endpoint of both efficacy and safety. Also, because the tolerability of a placebo may be high (toxicities low), in some instances a placebo arm may

have a good or respectable distribution for TTF. The difference on TTF between the control therapy and a placebo may be highly sensitive.

Genentech expressed understanding. They will still do the analysis, but not use it for labeling claims.

- e. For the sensitivity analysis for progression-free survival (PFS), we recommend a cutoff of 56 days (the length of time between tumor assessments) instead of a cutoff of 30 days. That is, if the patient dies more than 56 days after their last tumor assessment without a diagnosis of progressive disease, then that patient will have their PFS censored at the time of their last tumor assessment.

Genentech agreed to do so for a cutoff of 84 days. They stated that the 56 days is an error. Assessments are every 12 weeks, not every 8 weeks.

Additional Discussion Items:

Genentech asked if PFS is an adequate endpoint for full approval. FDA replied that it depends on the overall dataset and magnitude of PFS. For study E2100, Genentech will provide survival data at the time of the PFS analysis.

FDA Attendees:

Center for Drug Evaluation and Research

Office of Drug Evaluation VI

Division of Review Management and Policy

Sharon Sickafuse, M.S.

Division of Therapeutic Biological Oncology Products

Joseph Gootenberg, M.D.

Robert Justice, M.D.

Jeff Summers, M.D.

Office of Biostatistics

Biologic Therapeutics Statistical Staff

Mark Rothmann, Ph.D.

Sponsor Attendees:

Genentech, Inc.

Alex Bajamonde, Ph.D., Director, Oncology Biostatistics

Angela Gordon, Ph.D., Project Team Leader

Susan Griffing, Associate Director, Clinical Operations

Patricia Harada, M.P.H., Manager, Regulatory Affairs

Alan Hartford, Ph.D., Senior Biostatistician, Oncology Biostatistics

Scott Holden, M.D., Assistant Medical Director, Medical Affairs

Cheryl Madsen, Senior Manager, Regulatory Affairs

Todd Rich, M.D., Senior Director, Regulatory Affairs

Janey Skillings, M.D., Director, Medical Affairs

Roche

Cornelia Irl, Ph.D., Biostatistics Section Head

ECOG

Robert Grey, Ph.D., Group Statistician

George Sledge, M.D., Breast Committee Chair

NCI

Helen Chen, M.D., Senior Investigator

JoAnne Zujewski, M.D., Senior Clinician

Rec.
03/31/08
9:07AM

ACTION PACKAGE

STN BL: 125085/91

PRODUCT: Bevacizumab (Avastin)

SPONSOR: Genentech, Incorporated

LICENSE NUMBER: 1048

REVIEW TEAM:

RPM	Sharon Sickafuse
Clinical	Lee Pai-Scherf
Statistics	Hong (Laura) Lu
Promotional Labeling	Sean Bradley
Imaging	Scheldon Kress
Imaging	Barbara Stinson

ACTION PACKAGE CHECKLIST

Application Information		
BLA # 125085 NDA #	BLA STN# 125085/91 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: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 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. <input type="checkbox"/> 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. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		February 23, 2008
❖ Action Goal Date (optional)		
❖ Actions		
• Proposed action		X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		CR 4-8-06
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		X Requested in AP letter <input type="checkbox"/> Received and reviewed

Application Characteristics

Review priority: Standard 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 No
- This application is on the AIP Yes 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 Yes No
- Press Office notified of action Yes No
- Indicate what types (if any) of information dissemination are anticipated
 - None
 - FDA Press Release
 - FDA Talk Paper
 - CDER Q&As
 - Other ASCO burst

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).

<p><i>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.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (<i>indicate date for each review</i>)	R. Pazdur, 2-21-08 P. Keegan, 2-22-08
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (<i>indicate date</i>)	2-22-08
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	included N/A
❖ Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Medication Guide	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	N/A
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Labeling reviews that address only carton and container labels 	N/A
❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 2-13-08 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting/ADRA) (<i>indicate date of each review</i>)	7-6-06
❖ NDA approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ AIP-related documents	
<ul style="list-style-type: none"> • 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. (<i>Include certification.</i>)	X Verified

Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	2-8-08, 2-14-08
<ul style="list-style-type: none"> Incoming submission documenting commitment 	2-20-08
<ul style="list-style-type: none"> ❖ Outgoing correspondence (letters, emails, faxes, telecons) 	6-14-06 STN assignment letter 7-7-06 IR email 7-21-07 filing & DI letter 7-28-06 telecon 8-1-06 IR email 8-30-06 IR email 9-8-06 CR letter 12-12-06 MS letter from 11-2-06 mtg 2-12-07 AD letter on revised SAP 2-12-07 AD letter on IRF charter 3-5-07 AD letter revised mtg minutes 7-30-07 AD letter on revised SAP 7-31-07 AD letter on revised SAP & IRF charter 9-6-07 resubmission ack letter 9-21-07 IR email 9-23-07 IR email 9-28-07 IR email 10-8-07 IR email 10-10-07 IR email 10-12-07 IR email 10-16-07 IR email 10-17-07 IR email 10-21-07 IR emails (2) 10-23-07 IR email 10-24-07 IR emails (3) 11-28-07 AD telecon 11-28-07 IR email 12-10-07 IR email 1-2-08 IR email 1-16-08 IR email 2-8-08 IR email 2-12-08 revised PI 2-13-08 revised PI 2-14-08 revised PI 2-22-08 approval letter
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, email, etc. 	6-6-06 memo of priority review 6-6-06 review committee assignment memo 7-20-07 review of 5-9-07 submission (EGOG eligibility) 2-11-08 revised committee assignment memo
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	9-28-05
<ul style="list-style-type: none"> <ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	10-28-04
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	

❖ Advisory Committee Meeting	
• Date of Meeting	12-5-07
• 48-hour alert or minutes, if available	Minutes included
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Federal Register Notice included
CMC/Product Quality Information	
❖ CMC/Product review(s) <i>(indicate date for each review)</i>	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer <i>(indicate date for each review)</i>	
❖ BLAs: Product subject to lot release (APs only)?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Environmental Assessment (original and supplemental applications) (check one)	
• <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	2-20-08
• <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
• <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ NDAs: Microbiology reviews (validation of sterilization & product sterility) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not a parenteral product
❖ NDAs: Facilities inspection (include EER printout)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ BLAs: Facility-Related Documents	
• Facility review <i>(indicate date(s))</i>	
• Compliance Status Check (approvals only, both original and supplemental applications) <i>(indicate date, must be completed within 60 days prior to AP)</i>	X Requested 2-11-08 X Accepted 2-19-08 <input type="checkbox"/> Hold <input type="checkbox"/> Cleared from hold

Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	
❖ ECAC/CAC report/memo of meeting	
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	9-8-06, 2-22-08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	in clinical review
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	Medical imaging 9-8-06, 1-29-07, 7-26-07, 8-30-07
❖ Microbiology (efficacy) review(s) (<i>indicate date of each review</i>)	X Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	in clinical review
❖ Risk Management Plan review(s) (including ODS) (<i>indicate location/date if incorporated into another review</i>)	X None
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	X Not needed
❖ Clinical Inspection Review Summary (DSI)	X None requested
• Clinical studies (<i>include copies of DSI letters to investigators</i>)	
• Bioequivalence studies (<i>include copies of DSI letters to investigators</i>)	
❖ Statistical review(s) (<i>indicate date of each review</i>)	<input type="checkbox"/> None 12-22-06, 7-24-07 (2) 1-25-08
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	X None

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: 125085/91 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 CTD hybrid

Filing Meeting: Date 7/6/06 Committee Recommendation (circle one): File RTF

RPM: Beverly Cunnor 7/6/06
(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):

Part A - RPM

Part B - Product/CMC/Facility Reviewer(s): _____

Part C - Non-Clinical Pharmacology/Toxicology Reviewer(s): _____

Part D - Clinical (including Pharmacology, Efficacy, Safety, and Statistical)

Reviewers Hong Lu, Lee Pai Schorf

- Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

Content	Y	N	Final justification, action & status
Cover Letter	<input checked="" type="radio"/>	<input type="radio"/>	
Form 356h completed	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> If foreign applicant, US Agent signature.	<input type="radio"/>	<input type="radio"/>	
Comprehensive Table of Contents	<input checked="" type="radio"/>	<input type="radio"/>	
Debarment Certification with correct wording (see * below)	<input checked="" type="radio"/>	<input type="radio"/>	
User Fee Cover Sheet	<input checked="" type="radio"/>	<input type="radio"/>	
User Fee payment received	<input checked="" type="radio"/>	<input type="radio"/>	
Financial certification &/or disclosure information	<input checked="" type="radio"/>	<input type="radio"/>	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="radio"/>	<input type="radio"/>	
Pediatric rule: study, waiver, or deferral	<input checked="" type="radio"/>	<input type="radio"/>	
Labeling:	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> PI –non-annotated	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> PI –annotated	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> PI (electronic)	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> Medication Guide	<input type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> Patient Insert	<input type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> package and container	<input type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> diluent	<input type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> other components	<input type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> established name (e.g. USAN)	<input type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> proprietary name (for review)	<input type="radio"/>	<input type="radio"/>	

* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge..."

Content	Y	N	Final justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> legible	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/>	<input type="radio"/>	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/>	<input type="radio"/>	

Examples of filing issues	Yes?	No?	Other distribution, action & status
<input type="checkbox"/> protocols for clinical trials present	<input checked="" type="checkbox"/> Y	N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<input checked="" type="checkbox"/> Y	N	
companion application received if a shared or divided manufacturing arrangement	Y	N	
if CMC supplement:			
<input type="checkbox"/> description and results of studies performed to evaluate the change	Y	N	
<input type="checkbox"/> relevant validation protocols	Y	N	
<input type="checkbox"/> list of relevant SOPs	Y	N	
if clinical supplement:			
<input type="checkbox"/> changes in labeling clearly highlighted	<input checked="" type="checkbox"/> Y	N	
<input type="checkbox"/> data to support all label changes	<input checked="" type="checkbox"/> Y	N	
<input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	<input checked="" type="checkbox"/> Y	N	
if electronic submission:			
<input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	<input checked="" type="checkbox"/> Y	N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? no

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: _____
- Dates: _____

Recommendation (circle one) File RTF

RPM Signature: Sickafuse

Branch Chief concurrence: Karen 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]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Clinical overview [2.5]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="radio"/> Y <input type="radio"/> N	<i>previously submitted to BLA</i>
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y <input type="radio"/> N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Study Reports and related information [5.3]	Y <input type="radio"/> N	<i>previously submitted to BLA</i> <i>previously submitted to BLA</i> " "
<input type="checkbox"/> Biopharmaceutic	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Pharmacokinetics (PK)	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Pharmacodynamic (PD)	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Postmarketing experience	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Case report forms	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Individual patient listings (indexed by study)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Literature references and copies [5.4]	<input checked="" type="radio"/> Y <input type="radio"/> N	

Example of Filing Issue	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	

Example of Finding Issue	Yes	No/Action & Status
<input type="checkbox"/> summary reports reference the location of individual data and records	(Y) N	
<input type="checkbox"/> protocols for clinical trials present	(Y) N	
<input type="checkbox"/> all electronic submission components usable	(Y) N	
statement for each clinical investigation:		
<input type="checkbox"/> conducted in compliance with IRB requirements	(Y) N	
<input type="checkbox"/> 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	
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	
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	
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	<input checked="" type="radio"/> Y	<input type="radio"/> N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	<input checked="" type="radio"/> Y	<input type="radio"/> N	
adequate characterization of product specificity or mode of action	<input checked="" type="radio"/> Y	<input type="radio"/> 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	<input checked="" type="radio"/> Y	<input type="radio"/> N	
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	<input type="radio"/> Y	<input checked="" type="radio"/> N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="radio"/> Y	<input type="radio"/> N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAs & other electronic datasets complete & usable?		RIMs sites identified?		
	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> NR
E 2100	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> NR
AVF 0776g	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> NR
AVF 2119g	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input checked="" type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> 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).

Multiple horizontal lines for text entry.

Is clinical site(s) inspection (BiMo) needed?

No

Is an Advisory Committee needed?

Yes

Recommendation (circle one): File RTF

Reviewer: Lee Pai-schuy (signature/ date) July 4, 2006 Type (circle one): Clinical Clin/Pharm Statistical

Concurrence:

Branch Chief: (signature/ date)

Division Director: Patricia Keegan 7-6-2006 (signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y N	
Clinical overview [2.5]	Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	Y N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	Y N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y N	
Study Reports and related information [5.3]	Y N	
<input type="checkbox"/> Biopharmaceutic	Y N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
<input type="checkbox"/> Pharmacokinetics (PK)	Y N	
<input type="checkbox"/> Pharmacodynamic (PD)	Y N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Postmarketing experience	Y N	
<input type="checkbox"/> Case report forms	Y N	
<input type="checkbox"/> Individual patient listings (indexed by study)	Y N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y N	
Literature references and copies [5.4]	<input checked="" type="radio"/> Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y N	

Examples of filing issues	Yes?		If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	(Y)	N	
<input type="checkbox"/> protocols for clinical trials present	(Y)	N	
<input type="checkbox"/> all electronic submission components usable	(Y)	N	
statement for each clinical investigation:			
<input type="checkbox"/> conducted in compliance with IRB requirements	Y	N	
<input type="checkbox"/> 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)	
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	
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	
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
	Y	N	
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	
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 electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
E2100	(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

