FDA Briefing Document
Oncology Drug Advisory Committee Meeting

December 5, 2007

BLA STN 125085/91.018
Avastin® (bevacizumab)

Applicant: Genentech Inc.

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

Genentech, Inc. seeks approval for bevacizumab, to be used in combination with paclitaxel, for first-line treatment of locally recurrent or metastatic breast cancer. Efficacy results are obtained from a single phase trial (E2100) submitted in support of the proposed indication and are not supported by the results of AVF 2119g, a randomized study of bevacizumab in the second/third-line treatment of metastatic breast cancer.

The E2100 study is an open-label, randomized (1:1) trial that enrolled 722 patients who had not received prior chemotherapy for their locally recurrent or metastatic breast cancer. Patients were randomized to receive paclitaxel alone or paclitaxel plus bevacizumab. The primary efficacy endpoint is progression free survival, which for the purposes of expanded labeling claims was adjudicated by a blinded independent committee of radiologists and oncologist. Secondary endpoints are overall survival, objective response rate, duration of objective response, and QOL. The study is sponsored by the National Cancer Institute (NCI) and conducted by Eastern Cooperative Oncology Group (ECOG).

The addition of bevacizumab to paclitaxel resulted in a 5.5 month increase in median progression free survival (PFS) with no statistically significant improvement in overall survival based on IRF. Tumor response rate was higher with bevacizumab plus paclitaxel as compared to paclitaxel alone (48.9% versus 22.2%).

Collection of adverse events was limited to NCI CTC grade 3-5 events; there was a 20.2 % increase in grade 3-5 toxicity in the bevacizumab plus paclitaxel arm over paclitaxel alone. Bevacizumab's major safety issues are: hypertension, thromboembolic events, left ventricular dysfunction, myocardial infarction, gastrointestinal perforation and proteinuria. Death attributed to study drug by the FDA was 1.7% (6/363) in the bevacizumab plus paclitaxel arm when compared 0% (0/348) paclitaxel alone.

As part of the clinical development program for breast cancer, Genentech conducted a phase 3 study (AVF2119g) of capecitabine with or without bevacizumab in patients with disease progression after both anthracycline- and taxane-based regimens. A total of 462 patients were randomized 1:1 to receive capecitabine alone or capecitabine plus bevacizumab. This study failed to demonstrate a statistically significant effect on PFS and overall survival. The objective response rate was higher in the bevacizumab arm (19.8% vs. 9.1%), however the duration of response was shorter among responding patients in the combination arm compared to those who received capecitabine alone.

The key issue of this application is whether the significant improvement in PFS, in the absence of an improvement in overall survival, is a measure of direct clinical benefit that supports regular approval of bevacizumab plus paclitaxel for 1st-line treatment of patients with metastatic breast cancer.

The improvement of PFS, in the absence of an improvement in overall survival in breast cancer patients, must be weighted against the increased toxicity, including deaths associated with the administration of bevacizumab. The absence of activity of bevacizumab in the second and third line setting for breast cancer as evident in the results of the AVF2119g study must be taken into consideration.

ODAC advice is requested.

II. PROPOSED INDICATION

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.

III. DRUG DESCRIPTION

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.

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).

Approval for both colorectal and lung cancer indications were based on randomized clinical trials demonstrating a statistical improvement in overall survival.

IV. REGULATORY BACKGROUND

October 19, 2001	Study E2100 "A Randomized Phase III Trial of Paclitaxel versus Paclitaxel plus Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer" submitted by NCI to IND 7921. The study was not originally designed as a registration trial either by the NCI or Genentech, Inc.
May, October 2002	FDA provided comments to NCI outlining the deficiencies in the statistical analysis plan. FDA pointed out that the primary efficacy endpoint was not clearly identified and defined in the protocol.

October 28, 2004	Genentech requested meeting with FDA to discuss the adequacy of the study E2100 to support an expansion of the Avastin labeling claims. 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. Genentech asked if PFS would an adequate endpoint for full approval. FDA replied that it depends on the overall robustness and magnitude of PFS, Genentech was asked to provide survival data at the time of the PFS analysis.
April 5, 2005	Genentech submitted a revised Statistical Analysis Plan.
April 6, 2005	First planned ECOG interim efficacy analysis. 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 made public on April 14, 2005 by Genentech and presented at the May 2005 American Society of Clinical Oncology (ASCO) meeting.
September 28, 2005	A pre-sBLA meeting was held to discuss plans for Genentech to submit an efficacy supplement to their license application (sBLA) based on the results of E2100 study. The key issues and agreements were: • The FDA agreed that E2100 can form the basis of the primary efficacy evaluation of the sBLA in support of accelerated approval. • The FDA again expressed concerns regarding the open-label trial design and requested an independent radiology review for confirmation of the progression events. • Genentech proposed that the ECOG DMC analysis would form the primary analysis to support the sBLA, but the final Genentech analysis would be the primary source for labeling. FDA stated that an agreement of the proposed primary analysis population could not be reached prior to review of the data. FDA expressed concerns that agreement on plan for data analysis was not reached prior to public release of ECOG DMC interim results and that the DMC analysis used multiple cutoff dates in the analysis of PFS. • Because the endpoint of PFS would support an accelerated approval, Genentech was told to submit data on 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.

May 23, 2006 — Supplemental BLA was submitted for licensure of Avastin

September 8, 2006 — Review of the information and data by FDA determined that the information and data submitted to support the sBLA were inadequate for a final approval action (Appendix 1). FDA issued a complete discipline review letter. The key issues were:

- The data set submitted by Genentech to support the license application was incomplete, without a data cut-off date for efficacy and safety. 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. Genentech stated that patient information, safety and efficacy data collection and clean-up was still ongoing. The data submitted did not allow a full evaluation of efficacy.

- 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 study.

November 2, 2006 — FDA met with Genentech to discuss the issues detailed in the CR letter. Agreement was reached regarding the content and format of the resubmission. FDA agreed with Genentech's proposal to conduct an independent, blinded review of all 722 patients to verify the efficacy results. Agreement was reached that the primary regulatory endpoint would be PFS adjudicated by an independent review facility (IRF). Genentech was asked to submit the updated survival data at the time of resubmission.

August 23, 2007 — sBLA STN 125085/91 resubmitted for licensure of Avastin.

V. CLINICAL REVIEW

This sBLA is supported by the results of a single phase 3 study (E2100) sponsored by NCI and conducted by ECOG. The application also contains the results of a single phase 1/2 safety and pharmacokinetic study (AVF 0776g) and one randomized phase 3 study in metastatic breast cancer patients with disease progression following anthracycline- and taxane-based regimens (AVF2119g) intended to provide additional safety and pharmacokinetics information for bevacizumab.

A. E2100 STUDY

1. STUDY DESIGN

Description of Trial

Study E2100 was an open-label, phase 3, 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/m^2 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/m^2 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). Patients who discontinue paclitaxel may continue bevacizumab. There would be no crossover.

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, but may have received hormonal therapy.

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 (IRF) 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 Non-Protocol Therapy (NPT) prior to documented PD, censored at the time of last tumor assessment prior NPT
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 or NCI's Expanded Participation Project (EPP) Toxicity Form, the AdEERS database, and MedWatch data from ECOG.
- Adverse events were collected every cycle (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.

For the purpose of expanded labeling claim, the primary endpoint was PFS based on IRF assessment, as specified in the April 4, 2007 revised SAP. 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. PFS would be analyzed by the stratified Cox regression method with the pre-randomization stratification factors as stratification factors for the analysis.

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. The primary analysis for objective response rate would be performed using Cochran-Mantel-Haenszel test with the pre-randomization stratification factors as stratification factors only patients with measurable disease at baseline.

On May 2006, Genentech submitted the sBLA based on the results from the first interim analysis for efficacy conducted by ECOG which was deemed statistically significant and resulted in termination of the trial and public dissemination of study results. 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, 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 deaths occurred, the number of events that constituted full information required for the analysis of overall survival as stated in the primary SAP.

2. STUDY RESULTS

Enrollment Period:	December 21, 2001 – May 26, 2004
Data cutoff dates:	Efficacy – February 9, 2005
	Overall survival – October 21, 2006
	Safety – August 9, 2005 (October 30, 2006 for NCI AdEERS)

A total of 268 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.

Patient Demographic and Prior Treatment Characteristics

A total of 722 patients were randomized to the study. Patient characteristics of the ITT population are summarized in Tables 1. Randomization was 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).

Table 1. 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)

In regards to prior breast cancer treatment (Table 2), the majority of the patients (83.8%) received prior hormonal therapy, either in the adjuvant or metastatic setting. The majority of the patients (65.8%) had received adjuvant chemotherapy, with 50.4% of the patients have 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 2. 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)	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)

Conduct of the Trial

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

Protocol deviation: Protocol deviations as per ECOG and Genentech are shown in Table 3. Approximately 30% of the patients had one significant protocol deviation by either ECOG or Genentech. ECOG case evaluation forms to verify protocol deviation were unavailable in 33/722 patients. The most significant deviations were continuing treatment beyond progression (5.8%), stratification errors (7.1%) and initiation of non-protocol therapy prior to documented disease progression (15.7).

Table 3. 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	14 (4.1)	26 (7.4)	40 (5.8)
• Incorrect treatment arm given	1 (0.3)	2 (0.6)	3 (0.4)
• Others	10 (3)	11 ((3.1)	21 (3.0)
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	0
• 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.
Adapted from Applicants E2100 CSR Table 5 and Listing 16 2/3.

Scan Availability to IRF for PFS Assessment

Radiographic scans were retrospectively collected by Genentech and forwarded to the IRF for review. The number and percent of patients with any scan available to IRF are summarized in Table 4. In total, 73 patients (10.1%) did not have any radiographic images submitted to the IRF.

Table 4. Radiographic Scan Availability to IRF

	PAC n=354 (%)	PAC/BV n=368(%)	Total n=722(%)
Patients with one or more scans submitted to IRF	319 (90.1%)	330 (89.7%)	649 (89.9%)
Patients with no scans submitted to IRF	35 (9.9%)	38 (10.3%)	73 (10.1%)

The number of patients with completely missing radiographic images for the first year of study (from baseline to Cycle 12) is summarized in Table 5. In the PAC arm, the percent of patients with missing radiographic images ranges from 4.2% to 11.8% among those who were expected to have a scan visit. In the PAC/BEV arm, the percent of patients with missing radiographic images ranges from 3.0% to 8.8% among those who was expected to have a scan visit.

Table 5. Completely Missing Radiographic Images by Visit per IRF Randomized Patients with at Least One Scan Available to the IRF

Visit	PAC N=319 (%)		PAC/BV 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)

Efficacy Results

Progression Free Survival

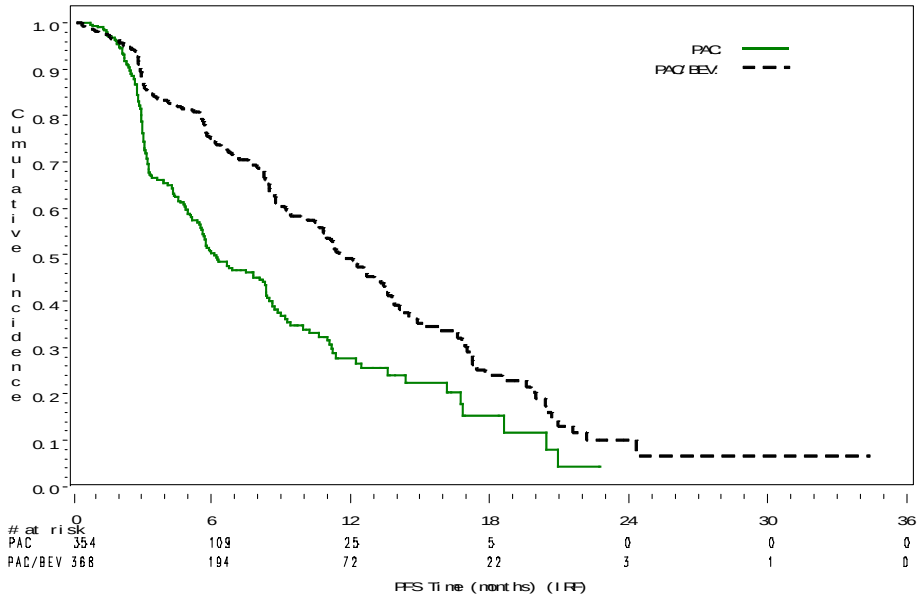
Progression Free Survival was adjudicated by a blinded independent review facility (IRF). Median PFS time was 11.3 months for the PAC/BV arm and 5.8 months for the paclitaxel alone group, (HR = 0.48, $p < 0.0001$). One hundred eighty four patients (52%) in the PAC arm and 173 patients (47%) in the PAC/BV arm had an event (Table 6, Fig 1)

Table 6. PFS Results based on IRF Assessments

	PAC (N=354)	PAC/BV (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 cut-off 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



The results presented in Table 6 and Figure 1 are based on the intent-to-treat (ITT) population including all randomized patients. The gold standard is an ITT analysis which requires all patients be followed until they reach their endpoint or until the end of study (data cutoff date). In study E2100, 34% of the patients had their IRF -determined PFS, censored more than 3 months (the time between two consecutively scheduled scans per protocol) before the data cutoff date.

Exploratory Analysis for (ECOG) investigator-determined PFS

An exploratory analysis for PFS based on ECOG assessment was conducted. The median PFS time was 11.4 months for the PAC/BV arm and 5.8 months for the paclitaxel 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/BV arm had an event. In this analysis, 17% of the patients had their ECOG-determined PFS censored more than 3 months (the time between two consecutively scheduled scans per protocol) before the data cutoff date.

Concordance/Discordance between IRF and ECOG in PFS Determination

The concordance between IRF and ECOG determination of PFS status (event/ no event) was assessed. As shown in Table 7, IRF and ECOG determinations of event status were discordant in a total of 174/722 patients (24%): 43 patients (12 in PAC arm and 31 in PAC/BV arm) were determined as progressed by IRF but as censored by ECOG; 131 patients (72 in PAC arm and 59 in PAC/BV arm) were determined as censored by IRF but as progressed by ECOG.

Table 7. Concordance/Discordance between IRF and ECOG in PFS Event Status

Treatment Arm	No. of discordance (%)		No. of concordance (%)
	IRF progressed ECOG censored	IRF censored ECOG progressed	
PAC	12 (3.4)	72 (20.3)	270 (76.3)
PAC/BV	31 (8.4)	59 (16.0)	278 (75.5)
Total	43 (6.0)	131 (18.1)	548 (75.9)

The concordance/discordance between IRF and ECOG determined PFS date is shown in Table 8. ECOG and IRF were discordant for 368 (181 in PAC arm and 187 in PAC/BV arm) patients, which accounts for 51.0% of the 722 patients.

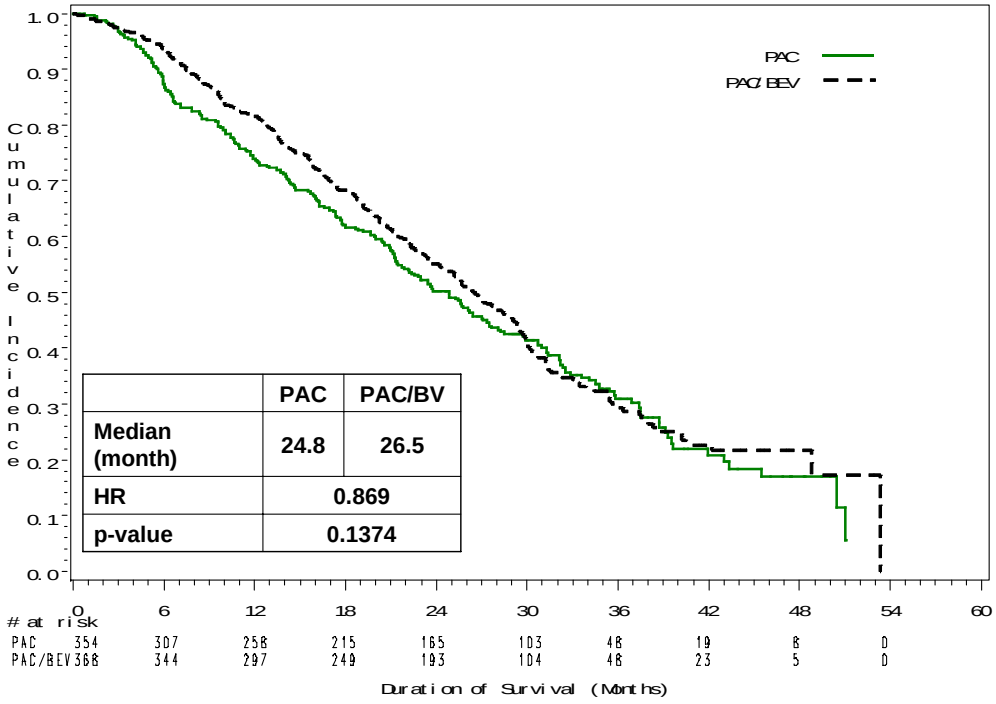
Table 8. Concordance/Discordance between IRF and ECOG in PFS Date

Treatment Arm	No. of discordance (%)	No. of concordance (%)
PAC	181 (51.1)	173 (48.9)
PAC/BV	187 (50.8)	181 (49.2)
Total	368 (51.0)	354 (49.0)

Survival

The overall survival results are shown in Figure 2. 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/BV arm). There was no statistically significant difference in the median OS PAC/BV arm (26.5 months) compared to the PAC arm (24.8 months) with the stratified log rank *p* value of 0.1374. The hazard ratio was 0.869.

Figure 2. Overall Survival



	PAC	PAC/BV
Median (month)	24.8	26.5
HR	0.869	
p-value	0.1374	

Post-Study Chemotherapy

Post-study chemotherapy information was not collected in the E2100 study

Objective Tumor Response

IRF assessed objective tumor response using RECIST criteria are shown in Table 9. Overall response rate was significantly higher in the PAC/BV arm when compare to PAC alone (48.9 % versus 22.2 %).

Table 9. Objective Response

	PAC N = 243 [a] (%)	**PAC/BV N = 229 [a] (%)**
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**	

a: include only patients with measurable disease at baseline
b: by the standard normal approximation.
c: 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).

Duration of Objective Response

Among the patients who achieved an objective response, the median duration of objective response was 9.7 months for the PAC arm and 9.4 months for the PAC/BV arm.

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 score from baseline to Week 17 for patients in arm A and B. Although the mean deterioration in QOL from baseline to Week 17 was statistically significant in favor of the PAC/BV arm, 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.

Safety

Extent of Drug Exposure

Because E2100 study did not capture the height, weight, or BSA or the patients, assumptions were made by the Applicant 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 10, patients in the PAC/BV received more paclitaxel in total, but with overall lower dose intensity than paclitaxel alone.

Table 10. 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% (12-105)	92.9% (38 – 145)

Adapted from Applicants CSR Table 14.3/1
^ 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 11).

Table 11. Dose Modification and Delays

	PAC N=348 (%)	PAC/BV N=363(%)	
Dose modification/omission	226 (64.9)	321 (88.4)	
Dose delay^ (≥ 1 week)	N=342 100 (29.2)	N=358 148 (41.3)	
Dose omission^	N=342	PAC N=358	BV N=358
	81 (23.7)	14 6 (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
^ Non-EPP patients only. Data from EPP patients are not available

Patients who Discontinued Treatment due to Toxicity/Side Effects/ Complications

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. 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 are: 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.

Incidence of Treatment Emergent Adverse Events

Because grade 1-2 toxicity was not systematically collected in the E2100 study, a comprehensive description and evaluation of all adverse events related to protocol therapy can not be made.

NCI-CTC Grade 3 -5 Adverse Events

The addition of bevacizumab to paclitaxel led to a 20.2 % increase in the per-patient incidence of grade 3-5 adverse events when compared to paclitaxel alone. The incidence of serious adverse events in the treatment arm is higher (71.1%) with NCI AdEERS reporting, however, because SAEs occurring in control arm were not required to be reported, a direct comparison can not be made.

Death attributed by investigators (ECOG) to treatment was higher in the PAC/BV arm when compared to the PAC alone arm (3.0 % versus 2.0 %). The incidence of death is higher (4.1%) when results submitted to the AdEERS reporting (refer to section regarding Death on Study below) are included.

The increased incidence of grade 3-5 adverse events in the PAC/BV arm was observed across all major organ systems: neurologic, cardiovascular, constitutional, gastrointestinal, infectious, renal, metabolic and pulmonary, hepatic, skin, musculoskeletal, and bleeding are highlighted in Table 13. In contrast, only thromboembolic events occurred at a higher incidence in the paclitaxel alone arm (4.3 % versus 2.5%).

Table 13. 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 4-5)	20 (5.7)	**50 (13.8)**	52 (14.3)
Metabolic/laboratory	15 (4.3)	**22 (6.1)**	23 (6.3)
Pulmonary/dyspnea	9 (2.6)	**16 (4.4)**	17 (4.7)
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 events observed in either arms was sensory neuropathy (24.2% in the PAC/BV arm versus 17.5 % 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. Genentech 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 10, Estimated Drug Exposure) and not intrinsic to bevacizumab therapy.

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 14 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 (Table 14).

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.

Deaths attributed to study drug toxicity are further discussed in the following section.

Table 14. 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)**

Deaths on Study

Table 15 shows all deaths reported for the study with ECOG/Genentech's attribution of cause of death. As expected, the majority of the patients died due to disease progression. Death was attributed by ECOG/Genentech to protocol treatment for one patient on the PAC arm; however, review of the CRF revealed that the patient died of bowel obstruction due to breast cancer. There were no deaths attributed to protocol treatment in the PAC/BV arm, by ECOG/Genentech in the sBLA submission.

Table 15 –Causes of Death

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)

Adapted from Applicant's CSR, Table 14.3/26
** Data presented is from ECOG CRF (cut off date August 9, 2005)*

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 Genentech and the FDA is shown in Table 16 and 17. Upon review of the case narratives and case report forms, the FDA disagrees with Genentech's "cause-of-death" attribution in several instances. Most importantly, in the PAC/BV arm, five out the twelve deaths were found to be possibly/definitively related to the protocol treatment (refer to Table 17 for summary of case narratives).

Table 16 – 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** **Probable**	0	0	0	 **2** **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's 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. A summary of case narratives and Genentech's attribution of the cause of death are shown in Table 17.

Table 17. Deaths on Study Possibly/Definitively Related to Protocol Therapy per FDA

Patient ID	Summary of Case Narratives
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 (Applicant's attribution: death due to breast cancer)
21258	64 years old patient, 6 cycles PAC/BEV, developed abdominal pain with gastrointestinal perforation, neutropenia, sepsis and death. (Applicant's attribution: death due to breast cancer)
21314	84 years-old patient, received 3 cycles of PAC/BEV, developed acute abdomen with gastrointestinal perforation, sepsis, respiratory failure and death. (Applicant's attribution: death due to other cause)
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 (Applicant's attribution: death due to other cause)
21403	73 years-old patient, 22 days after bevacizumab treatment developed progressive fatigue, pneumonitis, and fatal cardiac ischemia/infarction and LV dysfunction. (Applicant's attribution: death due to other cause)
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. The cardiac arrest was assed as possibly related to protocol therapy, pulmonary embolism and other unknown causes by NCI. (Applicant attribution: death due to other cause)

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. Patient ID # 21088 (PAC arm), was reported by Genentech as death "due to protocol treatment" but the CRF indicates the cause of death as due to small bowel obstruction caused by metastatic breast cancer.

B. AVF 2119 g Study

Summary Efficacy Results

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 (TP1) patients, 230 patients in the capecitabine alone arm and 232 patients in the capecitabine plus bevacizumab arm. Randomization was 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 taxane- treatment, either in the adjuvant or metastatic settings. Seventy patients were eligible for TP2 and continued bevacizumab with other therapy after disease progression (TP2).

The study failed to demonstrate a statistically significant effect on PFS and overall survival. The median PFS (Table 18) 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).

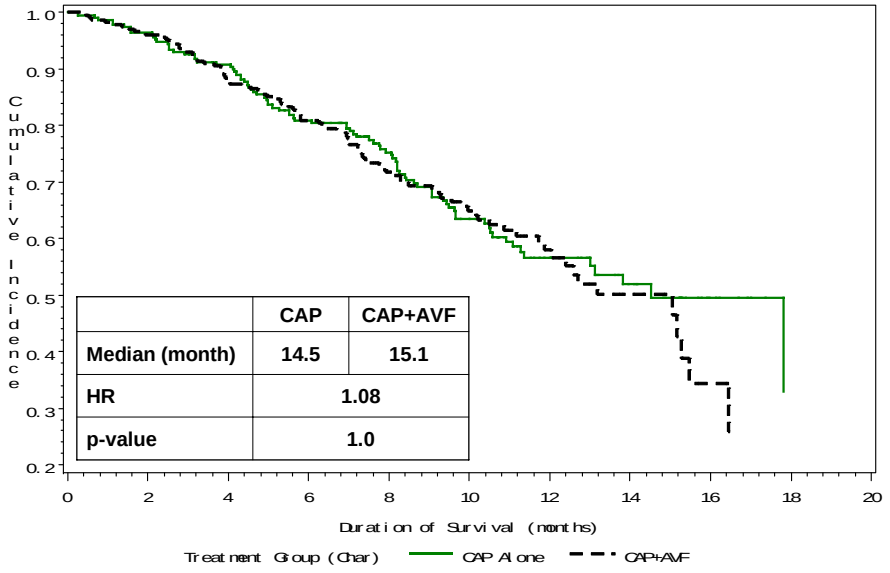
Table 18. Progression Free Survival (IRF/INV)

	Capecitabine (N=230)	Capecitabine + BEV (N=232)
Subjects with an event Disease Progression Death	126 (55%) 124 (54.1%) 2 (0.9%)	146 (63%) 143 (61.7%) 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 95% CI	 4.17 (3.71, 5.13)	 4.86 (4.17, 5.52)
Stratified Analysis[a] Hazard Ratio[b] 95% CI p-value (log-rank)	 - - -	 0.98 (0.77, 1.25) 0.857

[a] Stratification" 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

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 objective response rate was higher in the bevacizumab arm (19.8% vs. 9.1%).

Figure 3. Overall Survival



Safety Results from AVF2119g

The most common side effects observed in the AVF2119g trial are shown in Table 19. 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, hypertension, epistaxis and albuminuria.

Table 19. 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)

Adapted from Applicant's CSR table 14.3/6

Serious Adverse Events

Adverse events occurring with bevacizumab are shown in Table 20. 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 20. Adverse Events Known to Occur 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 and 72.5% (CAP+BEV) of the patients.

Thirty one patients died during the study period (21 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 TP2 (neutropenia, sepsis)

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

C. AVF0776g STUDY

AVF0766g is a phase 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 the 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%).

VI. DISCUSSION

The key issue of this sBLA for ODAC consideration is whether an estimated 5.5 month improvement in median PFS, with no statistically significant improvement in survival is adequate to support approval of bevacizumab with paclitaxel for first line treatment of patients with metastatic breast cancer.

Until recently, following ODAC's advice, the FDA's efficacy requirements for regular marketing approval for oncology drugs requires demonstration of clinical benefit, specifically, prolongation of life or better quality of life. Established surrogate endpoints such as durable complete remission (CR) in acute leukemias and disease-free survival (DFS) in adjuvant therapy for breast cancer have been accepted to support regular drug approval in these settings.

In May, 2004, gemcitabine in combination with paclitaxel received regular approval 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.

In contrast, it is noted that the final OS results of E2100 study is not statistically significant (hazard ratio of 0.869, stratified log rank p = 0.1374). The effect of adding bevacizumab to paclitaxel is observed in the 5.5 months improvement in PFS and a significant increase in objective tumor response rate. It should also be noted that bevacizumab in combination with capecitabine for second and third line breast cancer (AVF2119g) failed to demonstrate an improvement in PFS and OS.

In the E2100 study, PFS is clearly not a surrogate endpoint for survival in first line breast cancer. The question is whether PFS is an established surrogate for clinical benefit other than survival in this setting.

Hence, two important issues should be taken into consideration for this application:

The first issue is that the addition of bevacizumab to paclitaxel did not prolong survival. It might be argued that a bevacizumab survival effect, if it exists, is being obscured by subsequent treatment and/or crossover. Treatment crossover was specifically not allowed in the E2100 study. Because post protocol anti-cancer therapy information was not collected, any conclusions in this regard would be purely speculative.

It is important to stress that for FDA-approved therapeutic proteins and cytotoxic drugs for this and other settings, previous studies have demonstrated prolongation of life, in spite of a high rate of cross-over or subsequent therapy in pivotal trials. Two examples are Herceptin for first line treatment of HER2 positive metastatic breast cancer and Xeloda in combination with docetaxel, for second line metastatic breast cancer.

The second issue is that the addition of bevacizumab to paclitaxel resulted in a 20.2% increase in grade 3-5 toxicity and death in 1.7 % of the patients in the bevacizumab plus paclitaxel arm when compared to 0% for paclitaxel alone.

As discussed during the ODAC meeting of June 7, 1999 (Appendix 2), the requirement for a favorable effect on survival is important for proof of drug efficacy as well as demonstration of safety (toxicity). Because cytotoxic drugs (and some biologic agents such as bevacizumab) have substantial toxicity, it is not always possible to discern whether the cause of death is due to drug toxicity or tumor progression, or both. Survival is the net effect of deaths from both tumor and drug toxicity. Whether the lack of survival advantage observed in the E2100 and AVF2119g trials is due to the increased toxic effect of bevacizumab in breast cancer patients, is not known.

PFS if properly measured might be an acceptable endpoint which may confer patient benefit, however, the added toxicity must be taken into consideration and it cannot outweigh any kind of benefit that we might see.

VII. CONCLUSION

In study E2100, the Bevacizumab/paclitaxel combination added 5.5 months to median PFS with no apparent effect on survival at a cost of increase toxicity, mainly hypertension, proteinuria, arterial and venous thrombosis, congestive heart failure, bowel perforation and death.

VIII. RECOMMENDATION

Deferred, pending advice of the ODAC.

Appendix 1

September 8, 2006 FDA correspondence to Genentech: Complete Review Letter

Eight Pages Withheld

Appendix 2

Link to June 7, 1999 ODAC meeting transcripts

Pages 1 – 100 http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3521t1a.pdf
Pages 101-200 http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3521t1b.pdf
Pages 201-300 http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3521t1c.pdf
Pages 301-338 http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3521t1d.pdf