ONCOLOGY DRUGS
ADVISORY COMMITTEE MEETING
5 DECEMBER 2007

AVASTIN® (Bevacizumab)

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

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (cont'd)

Page

TABLES AND FIGURES

TABLE OF CONTENTS (cont'd)

Page

TABLE OF CONTENTS (cont'd)

Page

TABLE OF CONTENTS (cont'd)

Page

EXECUTIVE SUMMARY

OVERVIEW

Study E2100, which evaluated bevacizumab in combination with paclitaxel for the treatment of metastatic breast cancer (MBC), served as the primary basis for Genentech's supplemental Biologics License Application (sBLA). The study was conducted by the Eastern Cooperative Oncology Group (ECOG) and enrolled primarily in the U.S. It was based on a strong scientific rationale, including the importance of vascular endothelial growth factor (VEGF), the target of bevacizumab, in MBC.

Study E2100 was a strongly positive, multicenter, randomized, Phase III trial conducted by a preeminent oncology cooperative group. This trial was declared positive by the independent Data Monitoring Committee (DMC) at the first interim analysis based on clearly meeting its primary endpoint. The efficacy and safety analyses subsequently performed for the purposes of regulatory approval were conducted by Genentech in accordance with the Genentech Statistical Analysis Plan. The addition of bevacizumab to first-line paclitaxel resulted in a statistically significant and clinically meaningful improvement in the primary endpoint, progression-free survival (PFS) based on an independent review of radiographs (hazard ratio [HR] of 0.483; $p < 0.0001$), with a 5.5-month increase in median PFS (from 5.8 to 11.3 months). The PFS benefit was consistent across patient subgroups. The robustness of the PFS result was demonstrated by multiple sensitivity analyses, with benefit maintained even in two worst-case analyses. The HR for overall survival was 0.869 ($p = 0.1374$), and median survival was improved by 1.7 months, with a notable separation of the curves in the first 30 months of this trial. The safety profile for bevacizumab in Study E2100 was consistent with the profile established in previous trials in this and other indications. Thus, the risk–benefit profile was highly favorable in the MBC setting.

Regulatory precedence for PFS as an endpoint for approval in breast cancer has been established, as PFS has served as the primary endpoint for the approval of most of the chemotherapy agents and hormonal agents currently and recently approved for use in MBC.

Based on the data and justification provided in this document, Genentech believe that bevacizumab, in combination with paclitaxel, should receive full approval for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer.

BEVACIZUMAB

Bevacizumab, a highly specific, recombinant humanized monoclonal antibody (IgG1) directed against VEGF, provided validation of anti-angiogenesis as an effective approach in cancer therapy. Bevacizumab binds to and neutralizes VEGF. The importance of VEGF is scientifically well established in a variety of tumor types, including breast cancer. Bevacizumab (Avastin®) was the first anti-angiogenesis agent approved for the treatment of cancer. In the U.S., Avastin®, given in combination with intravenous 5-fluorouracil–based chemotherapy, is approved for the first- and second-line treatment of metastatic colorectal cancer and, in combination with carboplatin and paclitaxel, for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non–small cell lung cancer. Significant improvements in both overall and progression-free survival were demonstrated in each of these settings. Based on the results of Study E2100, Avastin® is also approved for the treatment of MBC in the European Union and 21 additional countries worldwide.

INDICATION

On 23 August 2007, Genentech submitted to the U.S. Food and Drug Administration (FDA) data in support of a sBLA requesting expansion of the Avastin® label to include the following 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.

BEVACIZUMAB STUDIES IN METASTATIC BREAST CANCER

The pivotal study, E2100, entitled “A Randomized Phase III Trial of Paclitaxel versus Paclitaxel plus Bevacizumab (rhuMAb VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer,” was sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and conducted by ECOG. This study compared paclitaxel (90 mg/m^2 weekly for

3 weeks and 1 week off) with paclitaxel + bevacizumab (10 mg/kg every other week) in the first-line treatment setting.

Study E2100 was designed to enroll approximately 685 patients to detect a 33% improvement in median PFS, from 6 to 8 months (HR = 0.75), with approximately 85% power. This sample size provided approximately 80% power, after 481 deaths were observed, to detect a 7-month improvement in median overall survival, from 24 to 31 months (HR = 0.77). Other endpoints included objective response rate, quality of life (QOL), and safety.

Three analyses of PFS were planned by ECOG at 50%, 78%, and 100% of information (corresponding to 270, 425, and 546 PFS events) using a one-sided O'Brien-Fleming boundary for the upper boundary and repeated confidence intervals for the lower boundary. The ECOG analysis was based on investigator-reported, ECOG-reviewed tumor assessments and was conducted by the ECOG DMC using analysis methods specified in the E2100 protocol.

At the first interim analysis (data cutoff date of 9 February 2005) performed on 6 April 2005, the ECOG DMC concluded that the primary endpoint of PFS had crossed the pre-specified O'Brien-Fleming boundary in favor of the paclitaxel + bevacizumab arm. When ECOG released the study results in April 2005, Study E2100 was fully enrolled; there was no change to the protocol to provide bevacizumab to patients in the paclitaxel alone arm.

ECOG transferred the database to Genentech following a period of data cleaning. The data were re-analyzed according to the Genentech Statistical Analysis Plan, with PFS based on investigator assessment as the primary endpoint (as ECOG had done). The original sBLA containing the Genentech analysis for Study E2100 was submitted to the FDA by Genentech on 23 May 2006. These results formed the basis of the worldwide approval of Avastin® for MBC.

On 8 September 2006, the Agency issued the Complete Response Letter. The following actions were taken after Genentech, ECOG, the NCI, and the FDA met on 2 November 2006:

- An independent review facility (IRF) was established, and radiographs and pertinent medical information for all patients were reviewed retrospectively to verify the primary endpoint of PFS for this open-label study.
- The primary endpoint of the study was changed to PFS based on the IRF's assessment of progression, given the inherent biases that may be present in unblinded PFS studies.
- Data cleaning of the E2100 database was completed.
- A survival sweep was conducted.
- Data cutoff dates for efficacy and safety were applied to the database.

The study data were re-analyzed by Genentech using the blinded, independent review of radiology and pertinent medical data by the IRF for assessment of disease progression and tumor response. The analysis was conducted according to a revised Genentech Statistical Analysis Plan, and the sBLA was resubmitted to the Agency on 23 August 2007.

Two other clinical trials conducted in patients with advanced breast cancer, Study AVF0776g and Study AVF2119g, were included in the application to provide supportive safety information per agreement with the FDA:

- Study AVF0776g was a proof-of-concept and dose-ranging, Phase II study in patients with previously treated MBC. The study demonstrated evidence of single-agent activity for bevacizumab (objective response rate of 6.7%) and supported the initiation of additional studies combining bevacizumab at a dose of 10 mg/kg every 2 weeks with chemotherapy for the treatment of patients with MBC.
- Study AVF2119g was a randomized, Phase III trial of capecitabine alone versus capecitabine + bevacizumab in MBC patients who had previously received both a taxane and an anthracycline. Most (85%) of the 462 randomized patients had previously received one or two lines of chemotherapy for metastatic disease prior to enrollment. A doubling of the objective response rate (from 9.1% to 19.8%) was observed, although Study AVF2119g failed to meet its primary objective of improving PFS.

EFFICACY RESULTS FOR E2100

A total of 722 patients were randomized to receive either paclitaxel alone (354 patients) or paclitaxel + bevacizumab (368 patients). The addition of bevacizumab to first-line paclitaxel for the treatment of patients with MBC resulted in a statistically significant and clinically meaningful improvement in PFS (HR = 0.483; $p < 0.0001$), with a 5.5-month increase in median PFS (from 5.8 to 11.3 months).

The primary and key secondary efficacy results are summarized in Table 1; the Kaplan–Meier curves for the primary endpoint of PFS are displayed in Figure 1.

Table 1

E2100 Primary and Key Secondary Efficacy Results:
Randomized Patients (Intent-to-Treat Analysis)

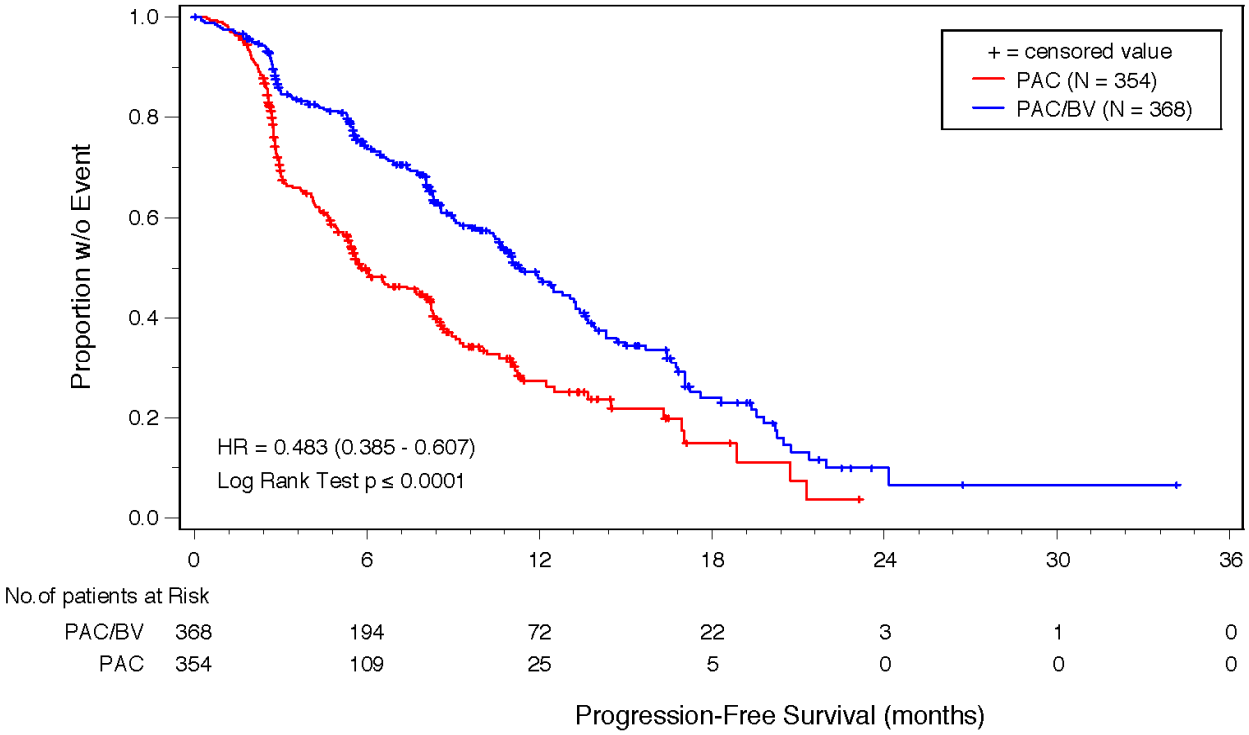
Endpoint	PAC (n=354)	PAC/BV (n=368)
Primary Endpoint		
Progression-free survival (months) based on the IRF review		
n	354	368
Median	5.8	11.3
HR		0.483
p-value	<0.0001	
Secondary Endpoints		
Overall survival (months)		
n	354	368
Median	24.8	26.5
HR		0.869
p-value		0.1374
Objective response rate (%) based on the IRF review		
n	243	229
Complete+partial responses (%)	54 (22.2%)	114 (49.8%)
p-value	<0.0001	
Duration of objective response (months)		
n	54	112
Median	9.7	9.4

HR=hazard ratio; IRF=independent review facility; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: Tumor assessment data are based on a 9 February 2005 cutoff date. Overall survival data are based on a 21 October 2006 cutoff.

The n for the PFS and overall survival endpoints represents the intent-to-treat population. The n for objective response includes only patients with measurable disease at baseline per the IRF; the n for duration of objective response includes only responders.

Figure 1
Progression-Free Survival Based on IRF Assessment: Randomized Patients



HR = hazard ratio; IRF = independent review facility; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

A consistent PFS benefit was observed in patient subgroups irrespective of age, prior therapy (anthracyclines or taxanes), disease-free interval, sites of disease or tumor burden (as measured by the baseline sum of longest diameters of all target lesions), and hormone receptor status, including triple-negative patients whose tumors did not express estrogen or progesterone receptors and did not overexpress the human epidermal growth factor receptor 2 (HER2).
The consistency of the PFS benefit across all subgroups supports the generalizability of the overall results.

When Genentech applied the same primary endpoint analysis to the investigator-reported, ECOG-reviewed progression data (rather than to the IRF data), patients who received paclitaxel + bevacizumab achieved a 5.6-month absolute increase in median PFS (from 5.8 to 11.4 months), with a HR of 0.421 ($p < 0.0001$), compared with those who received paclitaxel alone.
The consistency observed in the Genentech analysis between the PFS results

based on IRF data and those based on investigator-reported, ECOG-reviewed data served to validate the rigor of investigator assessments and the ECOG review process in this multicenter study. Agreement between the IRF and ECOG assessments of PFS status was 76.3% and 75.5% for paclitaxel alone and paclitaxel + bevacizumab arms, respectively. The agreement between the IRF and ECOG assessments of objective response status was 83.9% and 76.4% for the paclitaxel alone and paclitaxel + bevacizumab arms, respectively.
The patient-level agreement rates are similar to those observed in other recent studies that have formed the basis for U.S. approval in MBC and other cancers (Geyer et al. 2006; M39021 Rituximab Indolent sBLA).

The robustness of the PFS result was tested further by a variety of sensitivity analyses exploring the impact of missing data for IRF review, early discontinuation of treatment for toxicity, and administration of non-protocol therapy. The treatment benefit was preserved in all of these, including two worst-case analyses.

Secondary endpoints included overall survival, objective response rate, and QOL. The HR for overall survival in the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.869 (95% confidence interval [CI]: 0.722, 1.046), which corresponds to a 15% improvement in overall survival. The improvement in overall survival did not reach statistical significance ($p = 0.1374$). The 95% CI for the HR indicates that values between 0.722 and 1.046 are consistent with the observed data. A 1.7-month improvement was observed in median survival, from 24.8 to 26.5 months. The Kaplan–Meier curves separated early and remained separated for well over 2 years. Post-hoc landmark survival analyses demonstrated improvements in 1-year survival (74.0% vs. 81.4%; $p = 0.017$) and 2-year survival (50.1% vs. 55%; $p = 0.191$). These data provide further evidence in support of clinical benefit.

The objective response rate in patients with measurable disease at baseline as assessed by the IRF was significantly improved in the bevacizumab-containing arm (22.2% vs. 49.8%; $p < 0.0001$). Among all randomized patients with measurable disease who achieved an objective response, duration of objective response was similar between the two treatment arms (9.7 and 9.4 months for the paclitaxel alone and paclitaxel + bevacizumab arms, respectively).

Finally, mean deterioration in QOL from baseline to Week 17 for the paclitaxel + bevacizumab arm was less than that for the paclitaxel alone arm (−6.6 vs. −12.7, respectively), and the difference in the change from baseline between the two treatment arms was statistically significant (p = 0.0069). There is no evidence of additional QOL burden for patients in the bevacizumab-containing arm compared with those in the paclitaxel alone arm.

SAFETY

The safety profile of bevacizumab seen in Study E2100 was generally consistent with the established safety profile, as reported in the Avastin® Package Insert (provided in Appendix A). No new safety findings were identified. The addition of bevacizumab to paclitaxel resulted in an overall increase in the incidence of Grade 3–5 adverse events: 50.6% of patients in the paclitaxel alone arm versus 71.1% of patients in the paclitaxel + bevacizumab arm experienced at least one Grade 3–5 adverse event (see Table 2). Nearly all of this increase was in the incidence of Grade 3 hypertension and sensory neuropathy. Grade 3 hypertension rarely resulted in drug discontinuation and, according to the NCI Common Toxicity Criteria (NCI-CTC) definition, means that medical management such as starting or changing an anti-hypertensive agent is required. The higher incidence of sensory neuropathy reflects, in large part, the greater time on therapy.

Table 2
Adverse Events (Grades 3–5) by NCI-CTC Term, Regardless of Causality, Occurring at a ≥2% Higher Incidence in the Paclitaxel + Bevacizumab Arm vs. the Paclitaxel Alone Arm: Treated Patients

NCI-CTC Term	PAC (n=348)	PAC/BV (n=363)
Patients with at least one event	176 (50.6%)	258 (71.1%)
Neuropathy–sensory	61 (17.5%)	88 (24.2%)
Cerebrovascular ischemia	0 (0%)	9 (2.5%)
Hypertension	5 (1.4%)	58 (16.0%)
Headache	2 (0.6%)	13 (3.6%)
Bone pain	6 (1.7%)	14 (3.9%)
Nausea	5 (1.4%)	15 (4.1%)
Vomiting	8 (2.3%)	20 (5.5%)
Diarrhea	5 (1.4%)	17 (4.7%)
Dehydration	3 (0.9%)	12 (3.3%)
Fatigue	18 (5.2%)	39 (10.7%)
Infection without neutropenia	16 (4.6%)	33 (9.1%)
Infection with unknown ANC	1 (0.3%)	11 (3.0%)
Neutrophils	11 (3.2%)	21 (5.8%)
Rash/desquamation	1 (0.3%)	9 (2.5%)
Proteinuria	0 (0.0%)	11 (3.0%)

ANC = absolute neutrophil count; EPP = Expanded Participation Project; NCI AdEERS = National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC = National Cancer Institute Common Toxicity Criteria; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

Note: This table shows NCI-CTC Grade 3–5 non-hematologic and Grade 4 and 5 hematologic adverse events regardless of causality occurring at a higher incidence (≥2%) in the paclitaxel + bevacizumab arm vs. the paclitaxel alone arm. For the 11 treated EPP patients, only possibly related adverse events were available.

A data cutoff date of 9 August 2005 was applied to the ECOG database; a cutoff of 30 October 2006 was applied to the NCI AdEERS database.

Adverse events that have been previously associated with bevacizumab based on a higher incidence among bevacizumab-treated patients in other studies include Grade 3–5 hypertension, proteinuria, bleeding, arterial thromboembolic events (including both cerebrovascular and cardiac ischemia or infarction), venous thromboembolic events, congestive heart failure, gastrointestinal

perforation, and neutropenia in the setting of co-administration with myelosuppressive chemotherapy. As displayed in Table 3, most of these events were increased in incidence in patients receiving paclitaxel + bevacizumab relative to those receiving paclitaxel alone, as expected. There was no increase in the incidence of Grade 3–5 venous thromboembolic events with the addition of bevacizumab to paclitaxel, which is consistent with the findings from several other bevacizumab studies (see the Avastin® Package Insert provided in Appendix A).

Table 3
Summary of Categories of Adverse Events of Interest:
Treated Patients

	PAC (n = 346)		PAC/BV (n = 362)	
Category of Adverse Event	All Grades (3–5)	Grade 5	All Grades (3–5)	Grade 5
Hypertension	5 (1.4%)	0 (0.0%)	58 (16.0%)	0 (0.0%)
Proteinuria	0 (0.0%)	0 (0.0%)	11 (3.0%)	0 (0.0%)
Arterial thromboembolic events [a]	0 (0.0%)	0 (0.0%)	13(3.6%)	2(0.6%)
Venous thromboembolic events [a]	15 (4.3%)	0 (0.0%)	11 (3.0%)	0 (0.0%)
Hemorrhage [a]	1 (0.3%)	0 (0.0%)	8 (2.2%)	0 (0.0%)
Congestive heart failure [a]	1 (0.3%)	1 (0.3%)	8 (2.2%)	0 (0.0%)
GI perforations [a]	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (0.6%)

EPP = Expanded Participation Project; GI = gastrointestinal; NCI AdEERS = National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC = National Cancer Institute Common Toxicity Criteria; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

Note: This table includes all adverse events (Grade 3–5) regardless of causality. For 11 treated EPP patients, only possibly related adverse events were available. A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

[a] Each of the categories of adverse events consisted of a list of NCI-CTC terms as determined by Genentech clinical review.

CONCLUSION

In summary, the results of Study E2100 provide strong and clinically meaningful evidence of the clinical effectiveness and benefit of bevacizumab in combination with paclitaxel for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer. This adequately and

well-controlled, multicenter trial provided a rigorous assessment of PFS by a blinded, central IRF that demonstrated statistically persuasive findings of improved PFS (HR = 0.483; $p < 0.0001$). The magnitude of the increase in PFS (from 5.8 to 11.3 months) for patients randomized to paclitaxel + bevacizumab is clinically important for patients. Compared with historical data, the paclitaxel arm performed as expected. The median PFS of 11.3 months for patients randomized to paclitaxel + bevacizumab represents the longest PFS yet reported in any first-line clinical trial in MBC and the greatest absolute improvement in PFS (median PFS observed in randomized trials of chemotherapy for MBC has historically been in the range of 4 to 9 months). The results described above demonstrate the generalizability, the robustness, and the consistency of the PFS analysis

The HR for overall survival in the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.869 (95% CI: 0.722, 1.046; $p = 0.1374$), which corresponds to a 15% statistically non-significant improvement in overall survival. The objective response rate more than doubled (from 22.2% to 49.8%; $p < 0.0001$) with the addition of bevacizumab to paclitaxel. There was no additional QOL burden for patients in the bevacizumab-containing arm compared with those in the paclitaxel alone arm.

The observed safety profile was consistent with the known profile of bevacizumab, and no new safety signals were identified in this breast cancer population. The most frequent adverse events were manageable.

Analysis of the safety and efficacy data in total demonstrates a highly favorable risk–benefit profile for bevacizumab in combination with paclitaxel that supports full approval of bevacizumab for the treatment of locally recurrent and metastatic breast cancer.

1. INTRODUCTION

The following discussion will review the background of metastatic breast cancer (MBC), treatment options for patients with MBC, goals of therapy, and FDA approvals for MBC. The major points are the following:

- MBC remains an incurable disease, with many patients succumbing to their disease within 1.5 to 3 years of diagnosis.
- A multitude of treatment options exist for patients with MBC who are ready to begin chemotherapy. The sequential use of many lines of therapy is common practice. Treatment choices are often made based on a variety of individual factors, including tumor biology, host factors, and patient preference.
- Although a key goal for physicians and patients is to prolong survival in MBC, only a small number of the scores of randomized, Phase III clinical trials in patients with newly diagnosed MBC have conclusively demonstrated a survival benefit.

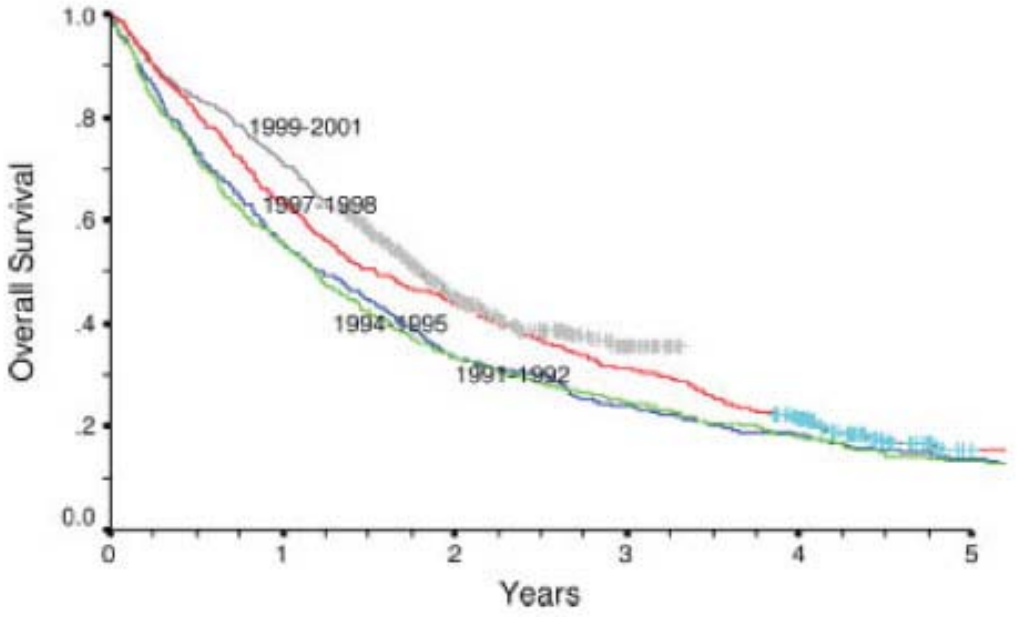
  A clinical trial that enrolls a first-line population expected to live 24 months, on average, with standard therapy would need to enroll enough patients to observe 2,000 deaths in order to demonstrate (with 80% power) an improvement of 3 months, consistent with a hazard ratio (HR) of 0.889.
- Maintaining or enhancing quality of life (QOL) is major goal of treatment. In practice and in clinical trials, QOL is generally inferred based on disease control (progression-free survival [PFS]), relief of disease-related symptoms, and toxicity. A longer duration of disease control may be associated with better overall QOL by delaying disease progression.
- Endocrine therapies and many of the chemotherapeutic agents have been granted full approval based on a PFS endpoint; some have shown a trend in overall survival.

1.1 BREAST CANCER BACKGROUND

Breast cancer is the most common cancer in women worldwide. Early detection and effective treatment of early-stage disease have led to a decline in mortality rates; however, it is estimated that more than 40,000 women will die of breast cancer in 2007 (American Cancer Society 2007). MBC remains an incurable disease, with many patients succumbing to their disease within 1.5 to 3 years of diagnosis. Over the past decade, incremental improvements in survival in the metastatic setting have occurred, as recent epidemiology data demonstrate

(Chia et al. 2007; see Figure 2). The authors attribute this to the availability and use of new chemotherapy and hormonal agents for the treatment of MBC.

Figure 2
Kaplan–Meier Curves for Overall Survival for Four Time Cohorts from Date of Diagnosis of MBC



Taken from Chia et al. 2007.

1.1.1 Current Treatment Options for Metastatic Disease

A multitude of tumor and patient factors are considered when deciding on a front-line treatment regimen, including the presence of hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]), presence of human epidermal growth factor receptor 2 (HER2) amplification, performance status, the extent of tumor burden, involvement of visceral organs, other medical conditions, and patient preference. Assessment with regard to HER2 and hormone receptor status in the context of prior adjuvant treatment has considerable impact on the selection and outcomes associated with treatment in the metastatic setting.

For patients who are unresponsive to hormonal agents and for those with shorter progression-free intervals and/or significant visceral disease, chemotherapy

becomes the treatment of choice, given the urgency to control disease and reduce symptoms.

Table 4 displays the recommended agents or regimens for the treatment of MBC based on the National Comprehensive Cancer Network (NCCN) Guidelines (NCCN Guidelines in Oncology: Breast Cancer 2007). Although the list appears extensive, the benefit to patients is somewhat limited by the fact that many patients are treated with the most active agents (anthracyclines and taxanes) in the adjuvant setting, with the consequence that metastatic disease will already have developed some degree of resistance. Overall, the number of agents (as shown in Table 4), combined with the use of trastuzumab, hormonal therapy, and polychemotherapy in the adjuvant setting, has the consequence that, in the metastatic setting, no single therapeutic approach has emerged that can be applied to all patients. The incurability of metastatic disease demands that new treatment strategies continue to be explored (Hamilton and Hortobagyi 2005), as this remains a disease of high unmet medical need.

Table 4
Adapted from the NCCN Guidelines (2007): Recommended Agents and Regimens for the Treatment of Metastatic Breast Cancer

First-Line Options (Chemotherapy)	Subsequent Lines (Chemotherapy)	Hormonal and Targeted Therapy
Docetaxel	Gemcitabine	Trastuzumab
Paclitaxel	Vinorelbine	Lapatinib
Abraxane® [a]	Paclitaxel	Exemestane
Doxorubicin + CTX	Capecitabine	Anastrozole
Epirubicin + CTX	Abraxane® [a]	Fulvestrant
Capecitabine	Docetaxel	Letrozole
Docetaxel + capecitabine	5-FU	Tamoxifen
5-FU + doxorubicin + CTX	CTX + methotrexate + 5-FU	Bevacizumab (with paclitaxel)
5-FU + epirubicin + CTX	Doxil® [b]	
Carboplatin + paclitaxel	Carboplatin	
CTX + methotrexate + 5-FU		
Paclitaxel + gemcitabine		

CTX = cyclophosphamide; 5-FU = 5-fluorouracil; NCCN = National Comprehensive Cancer Network.

[a] Paclitaxel protein-bound particles.

[b] Doxorubicin liposomal injection.

The availability of multiple chemotherapy agents and the demonstration that combination chemotherapy was superior to single-agent treatment drove the use of combination regimens throughout the 1980s and 1990s. This paradigm was challenged by the Phase III study E1193, which compared the outcome for newly diagnosed metastatic patients treated with a combination of the most active chemotherapy agents (doxorubicin + paclitaxel) with the outcome for those treated with these same agents on a sequential basis. Combination therapy was associated with a statistically significant improvement in PFS relative to either of the single-agent arms; however, there were no significant differences with regard to median overall survival or QOL. The authors concluded that, in the absence of true therapeutic synergy, sequential chemotherapy represented a reasonable option for patients with MBC. This finding has been reflected in clinical practice, in which the use of combinations of chemotherapy agents has shifted more toward the treatment of symptomatic patients with larger tumor burdens, in whom a rapid response is desired.

There are limited data regarding the optimal duration of any given chemotherapy for patients who have not progressed. This issue is of considerable importance, given that QOL for patients with MBC can be related both to the disease and to its treatment. Treatment regimens that are well tolerated and that can control disease symptoms for long periods of time may maintain QOL more effectively than shorter, more dose-intense regimens. In a study conducted in the 1980s, Coates and co-workers hypothesized that an approach of providing a limited duration of initial chemotherapy (intermittent chemotherapy) would improve QOL compared with continuous use of chemotherapy until disease progression. However, the results, as published in the New England Journal of Medicine (Coates et al. 1987), indicated a significant improvement in response rate (49% vs. 32%), time to disease progression (TTP; 6.0 vs. 4.0 months), and QOL for patients receiving chemotherapy continuously until disease progression. There was also a 1.3-month improvement in median overall survival, from 9.4 to 10.7 months (HR = 1.3; 95% confidence interval [CI]: 0.99, 1.6) for this group. These data support that a longer duration of disease control may be associated with better overall QOL. Several subsequent studies provided additional support for the concept of prolonged chemotherapy leading to better outcomes with regard to disease control, as measured by PFS (Gennari et al. 2006). More recently, Gennari and co-workers were not able to demonstrate an

improvement in progression-free or overall survival for patients randomized to receive maintenance paclitaxel after 6–8 cycles of anthracycline/taxane–based chemotherapy (Gennari et al. 2006). Optimal duration of therapy remains an open question, with trials ongoing.

1.1.2 Goals of Treatment

Because MBC is currently an incurable disease, the goal of treatment is to prolong survival and maintain QOL by minimizing disease- and treatment-related symptoms. However, only a small number of the scores of randomized, Phase III clinical trials in patients with newly diagnosed MBC have conclusively demonstrated a survival benefit (Smith 2006). This finding is no doubt multi-factorial, resulting from the confounding effect of subsequent treatment, the large sample size required to answer a survival question, and multiple other features. Interestingly, the trials that do show a survival benefit are often conducted in poor-risk patients who have a shorter median survival and who are perhaps less likely to receive subsequent treatment. A clinical trial that enrolls a first-line population expected to live 24 months, on average, with standard therapy would need to enroll enough patients to observe 2,000 deaths in order to demonstrate (with 80% power) an improvement of 3 months. This survival benefit would likely be considered clinically meaningful and would be consistent with a HR of 0.889.

Table 5 provides a summary of selected randomized, Phase III trials studying the efficacy of chemotherapy conducted in MBC since 2001, excluding trials of trastuzumab. PFS or TTP has been the primary endpoint in most of these trials given its ability to provide an objective measure of drug activity that is not confounded by subsequent treatment. In addition, for cytostatic drugs, PFS and TTP are endpoints that assess disease control in addition to tumor response. The PFS observed in these randomized trials of chemotherapy for MBC ranged from 4 to 9 months.

Maintaining or enhancing QOL is major goal of treatment. Multiple validated measures available; however, QOL analyses are often challenging because of missing data and the open-label nature of most oncology studies. In the first-line setting of MBC, many patients are still relatively asymptomatic, making it difficult to show a QOL improvement. The available QOL measures are imperfect,

and none are used routinely in clinical practice. In practice and in clinical trials, QOL is generally inferred based on disease control (PFS), relief of disease-related symptoms, and toxicity. QOL has been examined as a secondary endpoint in many trials in the metastatic setting. Significant QOL improvements have rarely been demonstrated.

Table 5

Summary of Recent Trials of Chemotherapeutic Agents in Metastatic Breast Cancer

Reference	Treatment	No. of Patients	Population	Primary Endpoint	Significant Difference in TTP/PFS	Significant Difference in OS
Jassem et al. 2001	AT vs. FAC	267	1st line	TTP	Yes	Yes
Biganzoli et al. 2002	AT vs. AC	275	1st line	PFS	No	No
O'Shaughnessy et al. 2002	D vs. XD	511	~30% 1st line ~70% 2nd line	TTP	Yes	Yes
Sledge et al. 2003	AT vs. T vs. A	739	1st line	TTF, RR	Yes (AT)	No
Nabholtz et al. 2003	AC vs. AD	429	1st line	TTP	Yes	No
Seidman et al. 2004	T q3wk vs. T qwk	585	1st line 2nd line HER2+	RR	Yes	No
Jones et al. 2005	D vs. T	449	2nd line	TTP	Yes	Yes
Zielinski et al. 2005	FEC vs. GET	259	1st line	TTP	No	No
Bontenbal et al. 2005	FAC vs. AD	216	1st line	TTP	Yes	Yes
Chan et al. 2005	XD vs. GD	305	1st line 2nd line	PFS	No	NR
Lueck et al. 2006	EP vs. XT	340	1st line	PFS	No	No
Muñoz et al. 2006	V vs. VG	256	1st–3rd line	PFS	Yes	NR
Vahdat et al. 2007	X vs. XI	752	1st–3rd line	PFS	Yes	NR
Alba et al. 2007	Observation vs. maintenance PLD	288	1st line	TTP	Yes	NR
Verill et al. 2007	T q3wk vs. T qwk	569	1st line	TTP	No	NR
Stockler et al. 2007	CMF vs. (continuous) vs. X (intermittent)	325	1st line	PFS	No	Yes
Melemed et al. 2007	T vs. GT	529	1st line	PFS/OS	Yes	Yes

A = doxorubicin; AC = doxorubicin/cyclophosphamide; AD = doxorubicin/docetaxel; AT = doxorubicin/paclitaxel; CMF = cyclophosphamide/methotrexate/fluorouracil; D = docetaxel; EP = epirubicin/paclitaxel; D = docetaxel; FAC = fluorouracil/doxorubicin/cyclophosphamide; FEC = fluorouracil/epirubicin/cyclophosphamide; GD = gemcitabine/docetaxel; GET = gemcitabine/epirubicin/paclitaxel; GT = gemcitabine/paclitaxel; NR = not reported; OS = overall survival; PFS = progression-free survival; PLD = doxorubicin liposomal injection; q3wk = every 3 weeks; qwk = every week; RR = response rate; T = paclitaxel; TTF = time to treatment failure; TTP = time to disease progression; V = vinorelbine; VG = vinorelbine/gemcitabine; X = capecitabine; XD = capecitabine/docetaxel; XI = capecitabine/ixabepilone; XT = capecitabine/paclitaxel.

1.1.3 FDA Approvals for Metastatic Breast Cancer

Many agents have been approved by the FDA for the treatment of MBC. The more recent approvals for chemotherapy and targeted agents are summarized in Table 6 (with the endpoints that served as the bases for regulatory approval in bold type); these include the taxanes (paclitaxel, docetaxel, and paclitaxel protein-bound particles; also known as Abraxane®), the epothelone derivative (ixabepilone), anti-metabolites (gemcitabine and capecitabine), and HER2-targeted agents (trastuzumab and lapatinib). Older FDA-approved agents for the treatment of MBC include methotrexate (1953), thiotepa and cyclophosphamide (1959), vinblastine (1961), 5-fluorouracil (1962), and doxorubicin (1974).

All of the approved drugs for the treatment of MBC have been granted full approval. All of the endocrine therapies have received full approval in the past decade for the treatment of MBC based on a progression endpoint. Many of the chemotherapeutic agents have also been approved based on a PFS endpoint, often with a trend in overall survival. This is especially true of gemcitabine, which is approved for the initial treatment of metastatic disease.

Trastuzumab and three of the modern chemotherapy agents (docetaxel, capecitabine, and gemcitabine) have demonstrated a statistically significant improvement in overall survival in patients with MBC, either at the time of initial approval or with additional follow-up.

Of the recently approved chemotherapies, only gemcitabine has received full approval for the treatment of a pure population of newly diagnosed metastatic patients. This was based on improvement in TTP (2.9 vs. 5.2 months; HR = 0.65; $p < 0.0001$) and a strong trend for improvement in overall survival in a Phase III trial of 529 patients. Recently, in an updated analysis of this trial, a 2.8-month improvement in median overall survival, from 15.8 to 18.6 months, was reported (HR = 0.82; 95% CI: 0.67, 1.00; p = 0.049; Melemed et al. 2007). This improvement was accomplished with an increase in hematologic toxicity (Grade 3 and 4 neutropenia was reported in 11.5% vs. 47.9% of patients treated with paclitaxel alone vs. paclitaxel + gemcitabine, respectively), Grade 3 and 4 fatigue, motor neuropathy, and transaminase elevations.

Table 6

FDA-Approved Cytotoxic and Targeted Therapies for Metastatic Breast Cancer from the Current Era

Agent/ Approval Date(s)/ Approval Type	Indication in MBC from Label (if applicable)	Endpoints Evaluated [a]		
		Response Rate	PFS/TTP Range	Survival Range
Paclitaxel (TAXOL®)/ October 1994/ Full approval	Indicated for treatment of breast cancer after failure with combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.	Paclitaxel 175 mg = 29% vs. paclitaxel 135 mg = 22% (p = 0.135)	**Paclitaxel 175 mg = 4.2 mo vs. paclitaxel 135 mg = 3.0 mo (p = 0.027)**	Paclitaxel 175 mg = 11.7 mo vs. paclitaxel 135 mg = 10.5 mo (p = 0.321)
Docetaxel (TAXOTERE®)/ May 1996, Accelerated Approval; June 1998/ Full approval [b]	Indicated for the treatment of patients with locally advanced or MBC who have progressed during anthracycline-based treatment or relapsed during anthracycline-based adjuvant therapy.	**Docetaxel = 28.1% vs. mitomycin/vinblastine = 9.5% (p < 0.0001)**	**Docetaxel = 4.3 mo vs. mitomycin/vinblastine = 2.5 mo HR = 0.75 (p = 0.01)**	**Docetaxel = 11.4 mo vs. mitomycin/vinblastine = 8.7 mo HR = 0.73 (p = 0.01)**
	Expanded to: Indicated for the treatment of patients with locally advanced or MBC after failure of prior chemotherapy in 1998. [b]	**Docetaxel = 45.3% vs. doxorubicin = 29.7% (p = 0.004)**	**Docetaxel = 6.5 mo vs. doxorubicin = 5.3 mo HR = 0.93 (p = 0.45)**	**Docetaxel = 14.7 mo vs. doxorubicin = 14.3 mo HR = 0.89 (p = 0.39)**
Capecitabine (XELODA®)/ 1998/ Accelerated approval; September 2001/ Full approval [b]	Indicated in combination with docetaxel for the treatment of patients with advanced or metastatic cancer after failure with prior anthracycline-containing chemotherapy.	Capecitabine/ docetaxel = 32% vs. docetaxel = 22% (p = 0.009)	Capecitabine/docetaxel = 186 days vs. docetaxel = 128 days HR = 0.643 (p = 0.0001)	**Capecitabine/docetaxel = 442 days (14.5 mo) vs. docetaxel = 352 days (11.5 mo) HR = 0.775 (p = 0.0126)**
	Indicated for the treatment of MBC resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline treatment is not indicated.			

HR = hazard ratio; IRF = independent review facility; MBC = metastatic breast cancer; NR = not reported; PFS = progression-free survival; TTP = time to disease progression.

[a] Endpoints that were the basis for the FDA marketing approval are indicated in bold (Johnson et al. 2003).

[b] Data shown are from studies used for full approval. Accelerated approval had been granted on objective response rate results.

[c] See respective package inserts.

[d] Summary basis of approval for lapatinib.

Table 6 (cont'd)

FDA-Approved Cytotoxic and Targeted Therapies for Metastatic Breast Cancer from the Current Era

Agent/ Approval Date(s)/ Approval Type	Indication in MBC from Label (if applicable)	Endpoints Evaluated [a]		
		Response Rate	PFS/TTP Range	Survival Range
Trastuzumab (HERCEPTIN®)/ September 1998/ Full approval	Indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Also indicated in combination with paclitaxel for treatment of patients whose tumors over express HER2 protein and who have not received chemotherapy for their metastatic disease.	Trastuzumab + all chemo = 45% vs. All chemo = 29%	**TTP Trastuzumab + all chemo = 7.2 mo vs. All chemo = 4.5 mo (p < 0.0001)**	**One-year survival rate Trastuzumab + all chemo = 79% vs. All chemo = 68% (p < 0.01)**
Gemcitabine (GEMZAR®)/ May 2004/ Full approval	Indicated in combination with paclitaxel for the first-line treatment of patients with MBC after failure with prior anthracycline-containing adjuvant therapy, unless anthracyclines were clinically contraindicated.	Gemcitabine/ paclitaxel = 40.8% vs. paclitaxel = 22.1% (p < 0.0001)	**Gemcitabine/paclitaxel = 5.2 mo vs. paclitaxel = 2.9 mo HR = 0.650 (p < 0.0001)**	**With median follow-up of 15.6 months, median survival, 12-, and 18-mo survival were increased and there was a strong trend toward improved overall survival for the gemcitabine/paclitaxel arm based on interim survival analysis [c]**
Paclitaxel protein-bound particles (ABRAXANE®)/ January 2005/ Full approval	Indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.	**Abraxane® 21.5% vs. paclitaxel 11.1% (p = 0.003) in all randomized patients**	NR	NR

HR = hazard ratio; IRF = independent review facility; MBC = metastatic breast cancer; NR = not reported; PFS = progression-free survival; TTP = time to disease progression.

[a] Endpoints that were the basis for the FDA marketing approval are indicated in bold (Johnson et al. 2003).

[b] Data shown are from studies used for full approval. Accelerated approval had been granted on objective response rate results.

[c] See respective package inserts.

[d] Summary basis of approval for lapatinib.

Table 6 (cont'd)

FDA-Approved Cytotoxic and Targeted Therapies for Metastatic Breast Cancer from the Current Era

Agent/ Approval Date(s)/ Approval Type	Indication in MBC from Label (if applicable)	Endpoints Evaluated [a]		
		Response Rate	PFS/TTP Range	Survival Range
Lapatinib (TYKERB®)/ March 2007/ Full approval	Indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy, including an anthracycline, a taxane, and trastuzumab.	Lapatinib/capecitabine = 23.7% vs. Capecitabine = 13.9%	**Lapatinib/capecitabine = 27.1 wk vs. Capecitabine = 18.6 wk HR = 0.57 (p = 0.00013)**	**Lapatinib/capecitabine = 55 deaths (28%) vs. Capecitabine = 64 deaths (32%) HR = 0.78 (p = 0.177)** [d]
Ixabepilone (IXEMPRA®)/ October 2007/ Full approval	Indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.	Ixabepilone/capecitabine = 34.7% vs. capecitabine = 14.3% (p < 0.0001) Monotherapy = 12.4% (by IRF)	**Ixabepilone/capecitabine = 5.7 mo vs. capecitabine = 4.1 mo (p < 0.0001)** **Monotherapy = 6.1 wk (by IRF)**	NR

HR = hazard ratio; IRF = independent review facility; MBC = metastatic breast cancer; NR = not reported; PFS = progression-free survival; TTP = time to disease progression.

[a] Endpoints that were the basis for the FDA marketing approval are indicated in bold (Johnson et al. 2003).

[b] Data shown are from studies used for full approval. Accelerated approval had been granted on objective response rate results.

[c] See respective package inserts.

[d] Summary basis of approval for lapatinib.

1.1.4 PFS as a Primary Endpoint for Regulatory Approval in Metastatic Breast Cancer Trials

Advantages of PFS as a primary endpoint include the lack of effect by crossover or subsequent therapies. However, disadvantages include the fact that PFS is not a statistically validated surrogate for overall survival in all settings, including first-line MBC. In addition, PFS is not precisely measured, requires balanced timing of assessments across treatment arms, and can be subject to assessment bias, particularly in open-label studies.

Recently, the FDA has reviewed with the Oncology Drugs Advisory Committee (ODAC) the acceptability of PFS or disease-free survival (DFS) as sufficient for full approval in a number of cancers, including colorectal cancer, lung cancer, and ovarian cancer. These discussions and recent approvals in the setting of renal cell cancer acknowledge that PFS can be considered a measure of clinical benefit.

A number of issues must be considered when PFS is used as an endpoint for regulatory approval. A finalized FDA guidance document (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007) outlines the advantages and disadvantages of tumor assessment endpoints, including PFS and TTP, and describes ways to improve the robustness of the data. According to the Guidance, in order to provide evidence acceptable for regulatory approval, a PFS primary endpoint requires a randomized trial design, preferably one that incorporated a placebo-controlled blind and an independent, blinded review of the endpoint. Per the Guidance, two judgments are deemed essential for evaluating the appropriateness of PFS as a primary endpoint:

- Whether PFS is acceptable for accelerated versus full approval. Major factors affecting this judgment include the magnitude of the effect size, the effect duration, and the benefits of other available therapy.
- An evaluation for bias or uncertainty regarding tumor assessment endpoints. Independent confirmation of the primary endpoint by a committee blinded to treatment is noted to be important, and essential in open-label trials.

The PFS results from Study E2100 met these criteria defined in the FDA Guidance, as outlined here:

- The magnitude of the effect of adding bevacizumab to paclitaxel and the impact on PFS are statistically persuasive (HR = 0.483; $p < 0.0001$).
- The median PFS among patients in the paclitaxel + chemotherapy arm (11.3 months) represents a high mark when compared with the paclitaxel alone arm (5.8 months) of Study E2100 and with historical trials, in which PFS of the experimental arm has ranged from 4 to 9 months, and thus clinically important.
- The rigorous independent review facility (IRF) assessment of the primary endpoint indicates that any bias entering into the trial as the result of the open-label design had minimal impact on the conduct of the study or the assessment of the primary endpoint of PFS.
- Treatment benefit was preserved in all of the extensive sensitivity analyses performed, including two worst-case analyses.

1.2 BEVACIZUMAB

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

1.2.1 Scientific Rationale and Mechanism of Action

Targeting tumor vasculature in human cancer as a treatment strategy is based on the observation that tumor growth is dependent on angiogenesis (Folkman 1990a, 1990b, 1995, 1997). In breast cancer, the density of microvessels in histologic specimens correlates with disease recurrence and survival (Weidner et al. 1991, 1992), demonstrating the clinical significance of angiogenesis in this tumor type. VEGF, a diffusible glycoprotein produced by normal and neoplastic cells, has been identified as a crucial regulator of both normal/physiologic and pathologic angiogenesis (Ferrara and Davis-Smyth 1997). Increased levels of VEGF expression have been found in most human malignancies examined to date (Ferrara and Davis-Smyth 1997; von Marschall et al. 2000; Luo et al. 2001) and have often been correlated with poor survival.

Bevacizumab selectively binds VEGF and prevents the interaction of VEGF with its receptors, thus neutralizing the biologic activity of VEGF (Presta et al. 1997).

A humanized IgG1 monoclonal antibody approach that inhibits VEGF function has several theoretical advantages. These include a high degree of specificity, prolonged drug half-life, and reduced risk of immunogenicity. Endothelial cells are genetically stable and therefore, in contrast to tumor cells, less likely to develop drug resistance during prolonged treatment. A combination of anti-angiogenic therapy and cytotoxic chemotherapeutic compounds that target tumor cells directly can potentially be complementary based on the different mechanisms of action underlying each strategy. Additionally, the ratio between cancer and endothelial cells within tumor tissue is approximately 10:1. Since a large number of tumor cells appear to be dependent on a relatively smaller number of endothelial cells, targeting VEGF inhibition may amplify the therapeutic effect of combination therapies. Finally, it is also likely that the metastatic spread of tumor cells is dependent on the existence of blood vessels within or adjacent to a tumor mass; thus, inhibition of angiogenesis may reduce tumor metastasis. On the other hand, angiogenesis may be driven by a combination of angiogenic signaling factors, especially in the most advanced disease settings. Because bevacizumab specifically targets VEGF, it may not be able to control disease when other pro-angiogenic factors overcome the effect of VEGF blockade alone. Nonetheless, clinical data confirming the activity of bevacizumab across a number of tumor indications validate the central role that VEGF can play in the malignant process.

1.2.2 Bevacizumab Clinical Development

a. General Clinical Development

Approximately three dozen comparative Phase III trials sponsored and conducted by Genentech, Roche, or the NCI have been completed or are underway throughout the world, testing bevacizumab in a wide variety of oncology indications, including early/adjuvant and advanced disease settings.

Based on an observed improvement in overall survival in Study AVF2107g, bevacizumab in combination with intravenous (IV) 5-fluorouracil (5-FU)–based chemotherapy was first approved by the FDA in February 2004 for the first-line treatment of patients with metastatic colorectal cancer (Hurwitz et al. 2004). Subsequent approvals in second-line colorectal cancer (20 June 2006) and non-squamous non–small cell lung cancer (11 October 2006) have been granted

by the FDA, again based on improvements in overall survival in Study E3200 (Giantonio et al. 2007) and Study E4599 (Sandler et al. 2006), respectively. In addition to Study E2100 in MBC (Miller et al. 2005a), an improvement in PFS was recently demonstrated in renal cell carcinoma (Yang et al. 2003; Escudier et al. 2007) in a Phase III study with PFS as the primary endpoint. Two Phase III studies, however, failed to meet their primary objectives, including Study AVF2119g (Miller et al. 2005b), described below, and Study C80303 in advanced pancreatic cancer (Kindler et al. 2007).

The overall safety profile of bevacizumab, as reflected in the Avastin® Package Insert (provided in Appendix A), is based on clinical trial data and post-marketing experience. Data have been analyzed for more than 10,000 patients who have received bevacizumab either as a single agent or in combination with chemotherapy or other therapies in completed clinical trials. Worldwide, it was estimated that as of February 2007, approximately 209,000 patients have been exposed to bevacizumab either as a marketed product or, in clinical trials, as an investigational agent.

b. Development in Metastatic Breast Cancer

Following the completion of Study E2100, eight additional comparative Phase III trials for patients with breast cancer have been initiated or planned, to be sponsored and conducted by Genentech, Roche, or the NCI. These include trials in the adjuvant setting, for patients with early-stage disease, and in the advanced disease settings. Bevacizumab is being evaluated in combination with various chemotherapy agents, with hormonal therapy, and for patents who overexpress HER2, with trastuzumab.

The supplemental Biologics License Application (sBLA) includes three clinical trials of bevacizumab conducted in patients with advanced breast cancer.

Study AVF0776g was a proof-of-concept, dose-ranging, Phase II study in patients with refractory MBC that evaluated the safety, efficacy, and pharmacokinetics of three different dose levels of single-agent bevacizumab (Cobleigh et al. 2003). This sequential dose-escalation study of bevacizumab was conducted in cohorts of patients receiving doses of 3, 10, or 20 mg/kg every other week. A total of 75 patients were treated (18, 41, and 16 patients,

respectively) between 11 November 1998 and 11 October 2000. Enrollment in the upper dose level (20 mg/kg every 2 weeks) was suspended because of toxicity after 16 patients had been treated at this dose level. The toxicity that led to termination of enrollment in the 20 mg/kg dose group was headache associated with nausea and vomiting, which occurred in 4 of 16 patients (25%) in this dose group. Other toxicities did not appear to be dose related, although there was a trend for a dose relationship in the average increases observed in pre-infusion systolic and diastolic blood pressures on Day 42 across the three dose groups. In addition to the headaches observed at the 20 mg/kg dose level, there were two reports of National Cancer Institute Common Toxicity Criteria (NCI-CTC) v2.0, Grade 3 left ventricular dysfunction (congestive heart failure [CHF] or cardiomyopathy). Both patients had prior anthracycline exposure and left chest wall radiation. Five of the 75 patients had an objective response (6.7%; 95% CI: 2.5%, 15.5%). The median duration of the five confirmed responses was 5.5 months, and individual durations of response were 2.3, 3.1, 3.7 (censored), 5.6, and 13.7 months.

Based on the activity observed with single-agent bevacizumab at a dose of 10 mg/kg every other week, two Phase III studies were initiated to further investigate bevacizumab in MBC. The additional MBC studies, AVF2119g and E2100, combined bevacizumab with chemotherapy.

Study AVF2119g was a Phase III, randomized, open-label, active-controlled trial designed to evaluate the safety, efficacy, and pharmacokinetics of bevacizumab in combination with capecitabine chemotherapy in patients with MBC who had been previously treated with both anthracycline- and taxane-based chemotherapies (Miller et al. 2005b). A total of 462 patients with MBC were randomized to one of two treatment arms: capecitabine alone at a dose of 2500 mg/m^2/day for 14 days of every 21-day cycle, or the same dose of capecitabine plus bevacizumab given at a dose of 15 mg/kg every 3 weeks until disease progression. Demographic and baseline characteristics were very similar in the two treatment arms. Approximately 44% of patients had received one prior chemotherapy regimen for MBC, and 40% had received two or more prior chemotherapy regimens for the treatment of metastatic disease. Fifteen percent of patients had not received prior chemotherapy for metastatic disease; this group of patients had received both agents in the adjuvant setting.

Approximately 23% of the patients overexpressed HER2. Notably, however, the protocol-specified regimen did not include a HER2-targeted agent.

The primary efficacy analysis did not demonstrate a statistically significant effect of bevacizumab treatment on PFS based on progression events assessed by the IRF. Median PFS was 4.17 months in the capecitabine alone arm and 4.86 months in the capecitabine + bevacizumab arm; the HR relative to capecitabine alone was 0.98, indicating no treatment benefit. Similar results were seen for PFS based on investigator assessment. Overall survival was comparable for the two treatment arms (14.5 vs. 15.1 months in the capecitabine alone and capecitabine + bevacizumab arm, respectively). The objective response rate, however, more than doubled with the addition of bevacizumab to capecitabine, as assessed by the IRF. The objective response rate was 19.8% in the capecitabine + bevacizumab arm compared with 9.1% in the capecitabine alone arm ($p = 0.001$) despite a lack of improvement in PFS or overall survival in this heavily pretreated population.

There are possible explanations for why Study AVF2119g failed to meet its endpoint. Study AVF2119g enrolled patients who overexpressed HER2 (23% of the study population), yet the regimen did not include a HER2-targeted therapy. Their disease may have been particularly refractory to any therapy that did not contain a HER2-targeted agent. Patients enrolled in Study AVF2119g were highly pretreated; 85% of the patients who were enrolled in Study AVF2119g had received chemotherapy for MBC prior to enrollment. Finally, the benefit of bevacizumab may be most apparent when combined with weekly paclitaxel, a drug that has inherent anti-angiogenic properties when given with this schedule and that has shown synergy with bevacizumab in nonclinical models.

Study E2100, entitled “A Randomized Phase III Trial of Paclitaxel versus Paclitaxel plus Bevacizumab (rhuMAb VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer,” was conducted by the Eastern Cooperative Oncology Group (ECOG). The primary endpoint was achieved at the first interim analysis of Study E2100, which demonstrated that PFS and objective response rate were statistically significantly increased when bevacizumab was added to first-line paclitaxel in patients with locally recurrent or metastatic breast cancer (Miller et al. 2005a). No new safety signals were

identified. The results of Genentech's analysis of Study E2100 formed the basis of a sBLA submitted to the FDA on 23 August 2007 (STN: BL125085-91). The Genentech analysis of Study E2100 was also submitted by Roche to the European regulatory agency in 2006; full approval was subsequently granted in the European Union in March 2007. The data from the sBLA submitted in August 2007 are the focus of this briefing book and are described in detail below.

1.2.3 Indication Sought

Based on the results of Study E2100, Genentech requests that Avastin®, in combination with paclitaxel, be indicated for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer. The proposed dose of bevacizumab is 10 mg/kg IV administered every 2 weeks until disease progression or unacceptable toxicity.

2. OVERVIEW OF STUDY E2100

Study E2100 was a multicenter, randomized, open-label, Phase III trial that evaluated the efficacy and safety of bevacizumab given in combination with paclitaxel to patients with locally recurrent or metastatic breast cancer versus paclitaxel alone.

2.1 ADMINISTRATIVE STRUCTURE

Study E2100 was sponsored by the NCI Cancer Therapy Evaluation Program (CTEP) and conducted by ECOG as an Intergroup study, in collaboration with nine other North American cooperative groups, including Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG), National Surgical Adjuvant Breast and Bowel Project (NSABP), National Cancer Institute of Canada (NCIC), North Central Cancer Treatment Group (NCCTG), Radiation Therapy Oncology Group (RTOG), Gynecologic Oncology Group (GOG), and participants in the NCI's Expanded Participation Project (EPP). Genentech was not involved in the conduct of the trial.

The ECOG DMC, which met twice each year, reviewed safety data as well as the results from the protocol-specified interim analysis of safety and efficacy.

2.2 E2100 REGULATORY HISTORY

The protocol for Study E2100 was written by ECOG and submitted to the FDA under the NCI's Investigational New Drug (IND) Application (BB-IND 7921) by the NCI on 19 October 2001. Time to treatment failure (TTF) had originally been selected as the primary efficacy endpoint for Study E2100 because the endpoint was believed to be a meaningful way to assess patient benefit and it would not be confounded by the multiple subsequent therapies that patients would likely receive during the course of their remaining lifetime.

On 21 December 2001, the study was activated under the original protocol, and the first patient was enrolled in January 2002. Enrollment was closed on 26 May 2004 following full accrual of the two treatment arms, with a total of 722 patients: 354 patients randomized to paclitaxel alone and 368 patients randomized to paclitaxel + bevacizumab. Overall, 88% of patients were enrolled at U.S. sites.

In May 2002, the FDA provided protocol review comments to ECOG regarding Study E2100. The FDA requested revisions to the E2100 protocol to address deficiencies in the statistical analysis section for the purpose of registration and identified the need for additional details regarding Genentech's pre-specified statistical analyses beyond those included in the protocol. ECOG amended the protocol (Addendum 4, dated 28 August 2003) based on the FDA's comments. Specifically, Section 9.0 (Statistical Considerations) was revised to describe the primary endpoint as PFS instead of time to treatment failure. A Statistical Analysis Plan (SAP; dated 24 September 2004), prepared by Genentech to support a possible regulatory filing, was submitted to the FDA. During a Type C teleconference between Genentech and the FDA on 28 October 2004, issues related to the adequacy of Study E2100 to support a label indication and the SAP were discussed. The FDA noted that the study design was not blinded to bevacizumab treatment and did not include an independent radiology review, and thus, the design would not allow for an unbiased assessment of progression. The FDA did state that the adequacy of PFS would depend on the overall dataset (i.e., the effect on survival) and on the magnitude of the PFS benefit. Additionally, the application would need to be reviewed prior to determining whether PFS could be used as an endpoint for full approval in breast cancer. Following the teleconference, Genentech submitted an amended SAP to the FDA on 5 April 2005; it did not include a plan to incorporate an independent radiology review.

The first efficacy interim analysis conducted by the ECOG DMC occurred in April 2005 (data cutoff date of 9 February 2005). The DMC determined that the primary endpoint of PFS, based on investigator-reported, ECOG-reviewed progression data, had met the pre-specified criteria for statistical significance for the comparison of paclitaxel + bevacizumab versus paclitaxel alone. Results of this interim analysis were made public by the NCI on 14 April 2005; however, no changes in study conduct occurred as a result of this finding. ECOG continued to follow the patients enrolled in the study as specified by the protocol, and there was no modification to the protocol; crossover was not offered to patients who had been randomized to the paclitaxel alone arm.

A Type B pre-sBLA teleconference meeting to discuss plans for Genentech to submit a sBLA was held on 28 September 2005. During this teleconference,

it was agreed that Study E2100 could form the basis of the primary efficacy evaluation for the sBLA.

A sBLA based on Study E2100 was submitted on 23 May 2006 for the additional indication of Avastin® in combination with taxane chemotherapy for the first-line treatment of recurrent or metastatic breast cancer. The Genentech analysis included all available data, as transferred to Genentech from ECOG at the end of 2005. Because the study had met its primary objective at the first interim analysis based on 50% of the required progression events, the analyses contained in the Genentech Clinical Study Report reflected that the study was ongoing, with patients still on therapy, and that ECOG was continuing to collect and clean the database.

The role of an independent radiology review of progression events in this open-label trial was again raised by the FDA during this review. At this time, the Agency requested an IRF review for a random subset of patients to validate the results and evaluate any potential for bias. Therefore, Genentech had begun in June 2006 to implement an IRF review for a subset of patients during the review. On 8 September 2006, the Agency issued a Complete Response Letter for the E2100 sBLA. One of the major issues was the need to complete the IRF review of the subjective PFS endpoint in a subset of patients. In addition, there was concern that the IRF review might not be completed with enough time to allow the FDA to review the results before the action date. The FDA also requested that there be additional cleaning of the E2100 database and application of a data cutoff date for efficacy and safety in a manner similar to that expected for an industry-sponsored trial.

On 2 November 2006, a Type A meeting between Genentech, representatives from the NCI, ECOG, and the FDA was held to discuss Genentech's proposed responses to the Complete Response Letter and to obtain agreement on the proposed contents of the resubmission. Key agreements included an independent and blinded review of all 722 patients conducted by an IRF in order to verify the efficacy results. This was accompanied by a change to the primary endpoint of the study from PFS based on investigator-assessed, ECOG-reviewed progression data to PFS based on the IRF-assessed progression data and agreements around the database cutoff dates for efficacy and safety; the overall

survival analysis would be based on full information of 481 events preceded by a sweep of survival information to ensure complete follow-up information. These agreements were reflected in the amended SAP submitted to the Agency on 4 April 2007.

After completing a re-analysis of an updated ECOG database and IRF database, Genentech resubmitted the sBLA to the FDA for review on 23 August 2007. Except where otherwise noted, the data in this briefing document are drawn from the E2100 sBLA. To provide supportive safety information, the Clinical Study Reports for Studies AVF0776g and AVF2119g accompanied the materials submitted to the FDA in August 2007 in Genentech's application for approval based on the analysis of Study E2100. However, no new analyses for the historical studies (AVF0776g and AVF2119g) were conducted.

2.3 STUDY OBJECTIVES AND DESIGN

2.3.1 Study Objectives

The primary objective of Study E2100 relevant to registration was as follows:

- To evaluate the efficacy of bevacizumab plus paclitaxel compared with paclitaxel alone in patients with chemotherapy-naive locally recurrent or metastatic breast cancer, as measured by PFS based on blinded, independent review of radiology and pertinent medical data by an IRF

The secondary objectives relevant to registration were as follows:

- To evaluate the objective response rate as assessed by the IRF, duration of response as assessed by the IRF, and overall survival with paclitaxel in combination with bevacizumab compared with paclitaxel alone
- To evaluate the toxicity of paclitaxel in combination with bevacizumab compared with paclitaxel alone
- To compare the quality of life (Functional Assessment of Cancer Therapy-Breast [FACT-B]) of patients treated with paclitaxel with that of the combination of paclitaxel plus bevacizumab as first-line therapy for MBC

The exploratory objectives contained in the Genentech SAP included the following:

- To compare PFS and objective response based on investigator-reported, ECOG-reviewed tumor assessments
- To compare TTF (IRF-assessed progression)

- To assess the effect of missing tumor assessments, inclusion of deaths within 84 days of the last tumor assessment, non-protocol therapy, and early discontinuation on the primary endpoint (IRF-assessed progression)
- To examine the effects of demographic and baseline prognostic characteristics on PFS and objective response rate as assessed by the IRF, and on overall survival

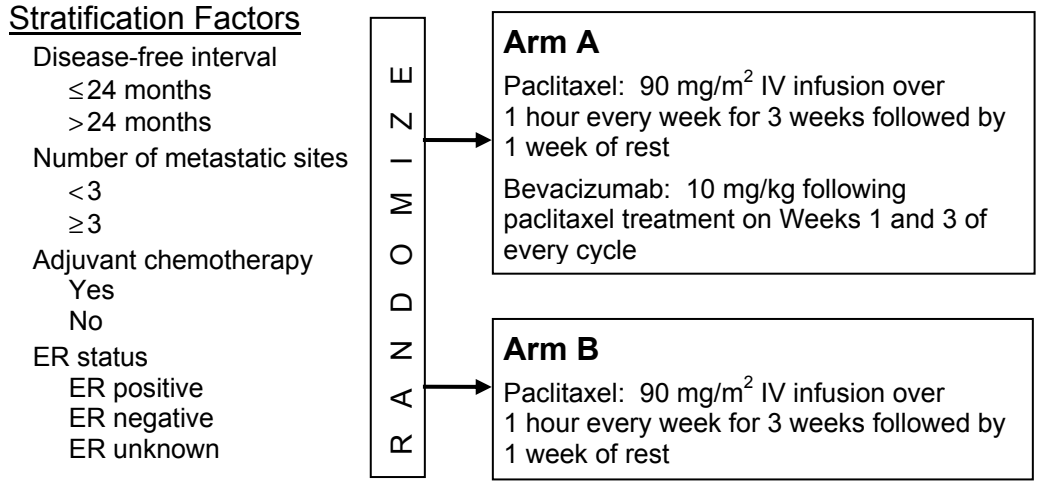
  The baseline prognostic characteristics (as reported in ECOG's E2100 database) include disease-free interval (≤ 24, > 24 months), number of metastatic sites (< 3, ≥ 3), adjuvant chemotherapy (yes, no), estrogen receptor (ER) status (positive, negative, and unknown), ECOG performance status at randomization (0, ≥ 1), age (< 40, 40–64, and ≥ 65 years), sex, race (White, non-White), baseline sum of the longest diameters of all target lesions, and HER2 expression status by immunohistochemistry.

2.3.2 Study Design

a. Overall Design and Study Plan

Patients were randomized in a 1:1 ratio to one of two treatment arms: paclitaxel + bevacizumab (Arm A) or paclitaxel alone (Arm B), as shown in Figure 3. 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).

Figure 3
Study Schema



ER=estrogen receptor; IV=intravenous.
Note: Doses were based on actual weight.

Protocol therapy was given in repeating 4-week cycles until disease progression, death due to any cause, or unacceptable toxicity. All patients were given IV paclitaxel (90 mg/m^2 over 1 hour) once a week for 3 weeks (i.e., at Weeks 1, 2, and 3 of each cycle), with no treatment given at Week 4. Patients in the paclitaxel+bevacizumab arm received IV bevacizumab every 2 weeks (i.e., on Weeks 1 and 3 of each cycle) until disease progression, death due to any cause, unacceptable toxicity, or (until the sixth protocol amendment on 9 March 2004) a maximum of 18 cycles of protocol therapy had been reached. Following Amendment 6, there was no upper limit to the number of cycles.

Agent-specific criteria for the discontinuation of paclitaxel and bevacizumab were specified in the protocol based on observed toxicity. Patients in the paclitaxel+bevacizumab arm who discontinued paclitaxel prior to progression were allowed to continue single-agent bevacizumab until disease progression. Similarly, they were allowed to continue single-agent paclitaxel if they discontinued bevacizumab prior to progression. Initiation of any non-protocol cancer therapy (NPT) given for the disease under study (breast cancer) prior to disease progression was reported. Thus, substitution of paclitaxel with an alternative cytotoxic agent prior to disease progression, although not explicitly prohibited by

the protocol, was reported as NPT. No information was collected on subsequent therapies following disease progression as assessed by the investigator.

All patients were to be followed for response and progression by physical and radiographic examinations (scans or X-rays) until disease progression, regardless of whether protocol therapy was discontinued prior to disease progression, and for survival for 5 years from the date of randomization. Patients, including those who discontinued protocol therapy prior to disease progression, were to be assessed for tumor progression and NPT until disease progression, and for toxicity every 12 weeks while on protocol therapy or, for patients who had discontinued protocol therapy, every 3 months for up to 2 years from randomization and every 6 months for 2 to 5 years from randomization.

Per the agreement with the FDA (Type A meeting dated 2 November 2006), all tumor assessment data, including pertinent medical information, were retrospectively reviewed by a blinded IRF according to the IRF Charter.

The protocol specified that the NCI-CTC v2.0 be used for toxicity and adverse event reporting. Grade 3–5 non-hematologic events and Grade 4 and 5 hematologic events were to be reported on the E2100 Toxicity Case Report Forms (CRFs; henceforth referred to as the E2100 Toxicity Form) at the end of every three cycles (12 weeks) for patients on protocol therapy. Additionally, adverse events meeting specific protocol guidelines, for patients randomized to paclitaxel + bevacizumab only, were to be reported in an expedited manner to allow for timely monitoring of patient safety. Following discontinuation of protocol therapy, treatment-related adverse events were collected every 3 months for patients who were < 2 years from randomization and every 6 months for those who were 2 to 5 years from randomization.

Once patients were > 5 years from randomization, only second primary cancer information related to treatment and treatment-related toxicities were to be reported.

b. Sample Size and Interim Analysis Plan per the ECOG Protocol

The protocol specified enrollment of approximately 685 patients who had not previously received chemotherapy for their locally recurrent or metastatic disease to achieve approximately 85% power to detect a 33% improvement in median

PFS, from 6 to 8 months. This sample size provided approximately 80% power after 481 deaths were observed to show a 7-month improvement in median survival, from 24 to 31 months (HR = 0.77).

Three ECOG analyses of PFS were planned at 50%, 78%, and 100% of information (corresponding to 270, 425, and 546 events) using a one-sided O'Brien-Fleming boundary for the upper boundary and repeated confidence intervals for the lower boundary. The ECOG analysis was based on investigator-reported, ECOG-reviewed tumor assessments and on analysis methods specified in the ECOG protocol. The results of these analyses, including safety data, were reviewed by the ECOG DMC.

2.3.3 Patient Selection

Patients with breast cancer that overexpressed HER2 (gene amplification as determined by fluorescent in situ hybridization or 3+ protein overexpression as determined by immunohistochemistry) were not eligible unless they had received prior therapy with trastuzumab. Patients must have had an ECOG performance status of 0 or 1, adequate organ function, and no evidence or history of central nervous system (CNS) metastases. Prior hormonal therapy for locally recurrent or metastatic disease was allowed, as was adjuvant or neoadjuvant taxane therapy, if completed ≥ 12 months prior to randomization. Other adjuvant therapy had to be discontinued ≥ 3 weeks prior to randomization.

2.3.4 Treatment Administration

a. Bevacizumab

Patients assigned to the paclitaxel + bevacizumab arm received bevacizumab after paclitaxel administered at a dose of 10 mg/kg IV at Weeks 1 and 3 of each 4-week cycle. Dose calculations were based on actual body weight at screening and were recalculated if a patient's weight changed by ≥ 10% during the study. The initial dose of bevacizumab was administered by IV infusion over 90 minutes; the rate was reduced to 60 and then 30 minutes for subsequent infusions if no infusion-associated adverse event (e.g., fever or chills) occurred with the previous infusion.

There was no dose reduction of bevacizumab specified in this study. Bevacizumab treatment was to be held based on the occurrence of certain protocol-specified grades and types of adverse events, graded according to NCI-CTC v2.0, including proteinuria, liver function test elevation, or investigator-defined, drug-related Grade 3 or 4 toxicity.

Patients were allowed to discontinue protocol therapy at any time. All patients who experienced disease progression were required to discontinue protocol therapy, including bevacizumab. In addition, patients were permanently discontinued from bevacizumab treatment for a number of protocol-specified events, including, but not limited to, uncontrolled or symptomatic hypertension; moderate or major bleeding that required hospitalization, transfusion, or intervention to control; a thrombotic event requiring treatment; or any Grade 3, 4, or new or worsening Grade 2 arterial thromboembolic (ATE) event.

If bevacizumab was discontinued because of toxicity, the patient could continue to receive paclitaxel alone as scheduled.

Bevacizumab Dose Selection

The dose of bevacizumab in this study was 10 mg/kg every 2 weeks, which is equivalent to a dose of 5 mg/kg/wk, the most commonly used dose of bevacizumab in clinical trials across multiple tumor types. In the Phase I/II, dose-escalation trial of single-agent bevacizumab for patients with MBC (Study AVF0776g), a dose of 10 mg/kg IV every 2 weeks was better tolerated than the higher dose of 20 mg/kg IV every 2 weeks and appeared to demonstrate clinical activity (Cobleigh et al. 2003).

b. Protocol-Specified Chemotherapy

Paclitaxel Dose and Administration

All patients received 90 mg/m^2 paclitaxel IV as a 1-hour infusion weekly for 3 weeks followed by 1 week of rest. Premedication with dexamethasone, diphenhydramine, and cimetidine or other H2 receptor antagonist was given 30–60 minutes prior to the paclitaxel infusion.

Paclitaxel Dose Selection

The protocol-specified control regimen of weekly paclitaxel was selected based on its significant activity and tolerability in patients with previously untreated MBC (Sledge et al. 2003). Nonclinical work also supported the potential for anti-angiogenesis activity from paclitaxel. The weekly schedule of paclitaxel would be expected to maximize any such potential, and thus, it had been hypothesized that paclitaxel might be synergistic when given with bevacizumab.

Paclitaxel Dose Modification and Discontinuation

The protocol provided a list of toxicities possibly associated with paclitaxel and specific instructions for holding, discontinuing, or dose reducing the chemotherapy if a patient experienced those toxicities. Paclitaxel treatment was discontinued for severe, life-threatening anaphylaxis or hypersensitivity reactions and for moderate symptoms that persisted with a reduced infusion rate. Other protocol-specified toxicities included neutropenia, thrombocytopenia, hepatic toxicity, neuropathy, or other toxicity thought to be related to drug. If paclitaxel was to be dose reduced, the 90 mg/m^2 dose was to be reduced to 65 mg/m^2. If this dose was not tolerated, paclitaxel was to be discontinued.

Patients randomized to the paclitaxel + bevacizumab arm who required discontinuation of paclitaxel could continue to receive bevacizumab as a single agent until disease progression.

2.4 DATA SOURCE AND CUTOFF DATES FOR THE GENENTECH ANALYSIS

The E2100 analyses presented below are based on the Genentech analysis of data from the ECOG database, tumor response and progression assessments from the IRF (RadPharm, Inc.), and additional adverse events (for the paclitaxel + bevacizumab arm only) reported to the NCI Adverse Event Expedited Reporting System (AdEERS) database.

Per agreement reached during the 2 November 2006 meeting with the FDA, the following cutoff dates were applied (see Table 7).

Table 7
Data Cutoff Dates for the Genentech Analysis of Study E2100

Cutoff Dates	Database Applied	Analyses Affected	Rationale for Cutoff Date
9 February 2005	ECOG and IRF	All efficacy analyses except overall survival	The cutoff date of the ECOG interim analysis that led to stopping the trial
21 October 2006	ECOG	Overall survival	The date overall survival matured (481 deaths)
No cutoff	ECOG	Cause of death	For the purpose of safety, no cutoff was applied
9 August 2005	ECOG	Safety analyses	Six months FU post–interim cutoff to provide more safety information
30 October 2006	NCI AdEERS [a]	Safety analyses	Twenty months FU post–interim cutoff to provide more safety information

FU = follow-up; IRF = independent review facility; NCI AdEERS = National Cancer Institute Adverse Event Expedited Reporting System.

[a] Available for the paclitaxel + bevacizumab arm only.

3. RESULTS OF STUDY E2100

3.1 STUDY PATIENTS

3.1.1 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.

A total of 258 centers enrolled patients in this study. Enrollment by center ranged from 1 to 37 patients. Most patients (88.8%) were enrolled at U.S. sites; however, participation of a small number of international sites occurred through collaborations with the cooperative groups. ECOG enrolled 65% of all patients, and another eight cooperative groups, along with the Expanded Participation Project (EPP), contributed the remaining 35% of patients in this study. Twelve patients were enrolled through the EPP.

Table 8 summarizes patient disposition and investigator-reported reason for treatment discontinuation for the intent-to-treat (ITT) population 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; 11 patients never initiated protocol therapy. Genentech verified that no treatment or toxicity data have been reported for any of these 11 patients.

Of the 711 treated patients, 664 patients (92.0%) had discontinued protocol therapy as of 9 August 2005, the cutoff date for treatment data. More patients had not yet discontinued protocol therapy in the paclitaxel + bevacizumab arm than in the paclitaxel alone arm (39 vs. 8 patients). The reasons for discontinuation other than disease progression/relapse during active treatment, as reported by investigators, were generally well balanced across treatment arms (see Table 8).

Table 8
Patient Disposition and Reasons for Protocol Therapy Discontinuation: Randomized Patients

Status and Reason for Protocol Therapy Discontinuation	PAC (n=354)	PAC/BV (n=368)	Total (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%)
Other [a]	61 (17.2%)	62 (16.8%)	123 (17.0%)
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%)

PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

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

[a] The most frequent reasons in the "Other" category included patient withdrawal or refusal, alternative therapy, other complicating disease, suspicion of progression, voluntary treatment break, or physician discretion.

3.1.2 Patient Eligibility and Protocol Deviations

a. Patient Eligibility

ECOG Eligibility Evaluation Forms were available for all randomized patients. Forty-nine patients (6.8%) were assessed as ineligible for the study by ECOG (see Table 9). The majority of the ineligible cases were the result of a radiology assessment conducted outside the protocol-specified 4-week window (24 of 49 patients) or a failure to discontinue prior hormonal or radiotherapy >3 weeks before the start of protocol therapy (14 of 49 patients).

Table 9
Eligibility as Assessed by ECOG:
Randomized Patients with an ECOG Eligibility Evaluation Form

	PAC (n = 354)	PAC/BV (n = 368)	Total (n = 722)
Patient eligible for this study (ECOG)			
Yes	325 (91.8%)	344 (93.5%)	669 (92.7%)
No	28 (7.9%)	21 (5.7%)	49 (6.8%)
Questionable	1 (0.3%)	3 (0.8%)	4 (0.6%)

PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

b. Protocol Deviations

ECOG reviewed each treated patient's data for pre-defined protocol deviations, such as incorrect treatment arm given and start of treatment prior to registration, captured on the ECOG Case Evaluation Forms. Typically, this review was completed only after the patient discontinued protocol therapy; thus, findings are available for approximately 689 patients (95%) enrolled in Study E2100. The proportion of patients with these deviations was generally well balanced across treatment arms (see Table 10).

Not included in Table 10 is the use of NPT prior to investigator-assessed, ECOG-reviewed disease progression, which was relatively well balanced across treatment arms (61 patients [17.2%] and 60 patients [16.3%] in the paclitaxel alone and paclitaxel + bevacizumab arms, respectively), as were the commonly administered types of NPT. The three most frequently administered classes of NPT, which constituted the majority of NPT administered, were chemotherapy, hormonal therapy, and palliative radiotherapy.

Table 10
Protocol Deviations: Randomized Patients

Protocol Deviation	PAC (n = 354)	PAC/BV (n = 368)	Total (n = 722)
No. of patients with a CRF [a]	340	349	689
Any protocol deviation	25 (7.4%)	39 (11.2%)	64 (9.3%)

CRF = Case Report Form; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.
[a] Protocol deviations as captured on an internal ECOG Case Evaluation CRF.

3.1.3 Patient Characteristics

a. Baseline Demographics

Demographic and baseline characteristics were balanced across the two treatment arms (see Table 11).

Table 11
Demographic and Baseline Characteristics: Randomized Patients

	PAC (n=354)	PAC/BV (n=368)	Total (n=722)
Age (yr)			
Mean (SD)	55.4 (11.5)	55.5 (11.7)	55.5 (11.6)
Median	55.0	56.0	55.0
Range	27–85	29–84	27–85
25th–75th percentile	47–63	47–64	47–64
Age category (yr)			
<40	32 (9.0%)	27 (7.3%)	59 (8.2%)
40–64	239 (67.5%)	257 (69.8%)	496 (68.7%)
≥65	83 (23.4%)	84 (22.8%)	167 (23.1%)
Race/ethnicity			
White	266 (75.1%)	284 (77.2%)	550 (76.2%)
Hispanic	19 (5.4%)	16 (4.3%)	35 (4.8%)
Black	35 (9.9%)	34 (9.2%)	69 (9.6%)
Other	34 (9.6%)	34 (9.2%)	68 (9.4%)
Menopausal status			
n	354	368	722
Premenopause	55 (15.5%)	63 (17.1%)	118 (16.3%)
Postmenopause	204 (57.6%)	195 (53.0%)	399 (55.3%)
Menopausal status not reported and age (yr)			
<50	28 (7.9%)	29 (7.9%)	57 (7.9%)
≥50	67 (18.9%)	81 (22.0%)	148 (20.5%)

PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab; SD=standard deviation.

b. Baseline Tumor Characteristics

Baseline characteristics related to tumor factors, as reported in the ECOG clinical database, are presented in Table 12. The two treatment arms were well balanced for nearly all factors based on data reported by the investigator.

Most patients (72.7%) had measurable disease, with a higher percentage of patients in the paclitaxel alone arm (77.1% vs. 68.5%). Only 1.7% of patients had locally recurrent disease as their sole site of disease, although 32.9% of patients had local–regional involvement. The most frequently involved metastatic sites were bone (54.5%), lung (41.5%), and liver (41.7%). A relatively small number of patients (8.7%) had bone metastases as their only reported site of metastatic disease. The majority of patients were ER-positive (61.8%) or both ER-positive and PR-positive (63.6%); 32.1% of patients were considered “triple negative” in that they tested negative for ER, PR, and HER2.

Three patients were reported as having brain metastases at baseline on the E2100 On-Study Form. All three were identified by ECOG as being ineligible. Two patients were withdrawn from the study prior to the start of protocol therapy. The third was discontinued from protocol therapy after receiving one dose of paclitaxel.

Table 12
Baseline Disease Status: Randomized Patients

	PAC (n=354)	PAC/BV (n=368)	Total (n=722)
Sites of involvement per ECOG CRF			
n	353	368	721
Local–regional	116 (32.9%)	121 (32.9%)	237 (32.9%)
Opposite breast	8 (2.3%)	6 (1.6%)	14 (1.9%)
Distant nodes	113 (32.0%)	121 (32.9%)	234 (32.5%)
Bone	192 (54.4%)	201 (54.6%)	393 (54.5%)
Lung	146 (41.4%)	153 (41.6%)	299 (41.5%)
Liver	157 (44.5%)	144 (39.1%)	301 (41.7%)
Pleura	57 (16.1%)	65 (17.7%)	122 (16.9%)
Brain and other CNS	2 (0.6%)	1 (0.3%)	3 (0.4%)
Other	67 (19.0%)	68 (18.5%)	135 (18.7%)
Number of involved sites			
n	353	368	721
Mean (SD)	2.5 (1.2)	2.5 (1.3)	2.5 (1.3)
Median	2.0	2.0	2.0
Range	1–7	1–8	1–8
25th–75th percentile	2–3	2–3	2–3
Number of involved sites category			
n	354	368	722
<3	184 (52.0%)	208 (56.5%)	392 (54.3%)
≥3	170 (48.0%)	160 (43.5%)	330 (45.7%)
Breast cancer type			
n	353	368	721
Locally recurrent	4 (1.1%)	8 (2.2%)	12 (1.7%)
Metastatic	349 (98.9%)	360 (97.8%)	709 (98.3%)

CNS=central nervous system; CRF=Case Report Form; ER=estrogen receptor; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab; PR=progesterone receptor; SD=standard deviation; SLD=sum of longest diameters of target lesions.

Table 12 (cont'd)
Baseline Disease Status: Randomized Patients

	PAC (n=354)	PAC/BV (n=368)	Total (n=722)
Number of metastatic sites			
n	354	368	722
<3	252 (71.2%)	262 (71.2%)	514 (71.2%)
≥3	102 (28.8%)	106 (28.8%)	208 (28.8%)
Bone-only disease			
n	353	368	721
Yes	27 (7.6%)	36 (9.8%)	63 (8.7%)
No	326 (92.4%)	332 (90.2%)	658 (91.3%)
ER status			
n	354	368	722
Negative	127 (35.9%)	138 (37.5%)	265 (36.7%)
Positive	223 (63.0%)	223 (60.6%)	446 (61.8%)
Unknown	4 (1.1%)	7 (1.9%)	11 (1.5%)
PR status			
n	354	368	722
Negative	182 (51.4%)	184 (50.0%)	366 (50.7%)
Positive	158 (44.6%)	166 (45.1%)	324 (44.9%)
Unknown	14 (4.0%)	18 (4.9%)	32 (4.4%)
ER/PR			
n	354	368	722
ER+ or PR+	227 (64.1%)	232 (63.0%)	459 (63.6%)
All others	127 (35.9%)	136 (37.0%)	263 (36.4%)
HER2 status by FISH			
n	350	367	717
Non-amplified	109 (31.1%)	108 (29.4%)	217 (30.3%)
Amplified	5 (1.4%)	2 (0.5%)	7 (1.0%)
Not done	236 (67.4%)	257 (70.0%)	493 (68.8%)

CNS=central nervous system; CRF=Case Report Form; ER=estrogen receptor; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab; PR=progesterone receptor; SD=standard deviation; SLD=sum of longest diameters of target lesions.

Table 12 (cont'd)
Baseline Disease Status: Randomized Patients

	PAC (n=354)	PAC/BV (n=368)	Total (n=722)
HER2 status by IHC			
n	353	367	720
0	167 (47.3%)	177 (48.2%)	344 (47.8%)
1+	82 (23.2%)	94 (25.6%)	176 (24.4%)
2+	33 (9.3%)	32 (8.7%)	65 (9.0%)
3+	4 (1.1%)	7 (1.9%)	11 (1.5%)
Not done	67 (19.0%)	57 (15.5%)	124 (17.2%)
HER2 status by FISH/IHC			
n	354	368	722
Negative	316 (89.3%)	334 (90.8%)	650 (90.0%)
Positive	6 (1.7%)	9 (2.4%)	15 (2.1%)
Unknown	32 (9.0%)	25 (6.8%)	57 (7.9%)
ER/PR/HER2 combined status			
n	354	368	722
Negative	110 (31.1%)	122 (33.2%)	232 (32.1%)
Disease-free interval			
n	354	368	722
≤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	354	368	722
n			
Yes	273 (77.1%)	252 (68.5%)	525 (72.7%)
No	81 (22.9%)	116 (31.5%)	197 (27.3%)
SLD (mm)			
n	274	253	527
Mean (SD)	78.8 (59.3)	82.3 (63.1)	80.5 (61.1)
Median	64.5	68.0	66.0
Range	10–357	12–350	10–357
25th–75th percentile	36–100	32–110	35–102

CNS=central nervous system; CRF=Case Report Form; ER=estrogen receptor; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab; PR=progesterone receptor; SD=standard deviation; SLD=sum of longest diameters of target lesions.

Prior cancer treatments reported for all randomized patients were well balanced across the two treatment arms (see Table 13). Overall, 65.8% of patients received adjuvant chemotherapy and 47.5% received adjuvant hormonal therapy. Adjuvant chemotherapy consisted of prior taxane therapy in approximately 20% of the patients and prior anthracycline therapy in approximately 50% of the patients.

Table 13
Prior Therapy: Randomized Patients

	PAC (n=354)	PAC/BV (n=368)	Total (n=722)
Prior systemic therapy			
n	354	368	722
Adjuvant hormonal therapy	175 (49.4%)	168 (45.7%)	343 (47.5%)
Metastatic/recurrent hormonal therapy	128 (36.2%)	134 (36.4%)	262 (36.3%)
Adjuvant chemotherapy (including high dose)	231 (65.3%)	244 (66.3%)	475 (65.8%)
Chemotherapy for metastasis or recurrence (including high dose)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Other	62 (17.5%)	71 (19.3%)	133 (18.4%)
Prior taxane therapy			
n	354	368	722
Yes	68 (19.2%)	74 (20.1%)	142 (19.7%)
No	286 (80.8%)	294 (79.9%)	580 (80.3%)
Prior anthracycline therapy			
n	354	368	722
Yes	180 (50.8%)	184 (50.0%)	364 (50.4%)
No	174 (49.2%)	184 (50.0%)	358 (49.6%)

PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

3.2 EFFICACY RESULTS

3.2.1 Primary Efficacy Endpoint: Progression-Free Survival Based on IRF Assessment

a. Primary Analysis of PFS

For the purpose of regulatory approval, the primary efficacy outcome measure for Study E2100 was Genentech's analysis of PFS based on disease progression as assessed by the IRF. The analysis population was the ITT population,

which consisted of all randomized patients. The analysis was based on a data cutoff date of 9 February 2005, the cutoff for the first interim analysis, which represents a minimum of 8 months of follow-up since the close of enrollment on 26 May 2004.

The primary efficacy analysis for this trial compared PFS based on IRF-assessed progression events between the paclitaxel + bevacizumab arm and the paclitaxel alone arm. PFS was defined as the time from randomization until disease progression or on-study death from any cause. On-study death was defined as death prior to 84 days after the last dose of protocol therapy. If no data were available for the IRF review, PFS was censored at randomization plus 1 day. For patients who did not have disease progression as determined by the IRF prior to the cutoff date of 9 February 2005, PFS was censored at the date of the patient's last tumor assessment in the IRF database. Finally, data for patients who initiated NPT prior to experiencing documented disease progression were censored at the time of the patient's last tumor assessment prior to initiation of NPT.

PFS was compared between the two treatment arms using a two-sided stratified log-rank test. The stratification factors for the log-rank test consisted of the four stratification factors used for patient randomization: disease-free interval (≤ 24, > 24 months), number of metastatic sites (< 3, ≥ 3), adjuvant chemotherapy (yes, no), and ER status (positive, negative, and unknown). The overall type I error rate for the two-sided test of PFS was controlled at $\alpha = 0.05$.

Among the 722 randomized patients, 357 IRF-reviewed progression events had occurred in the two treatment arms (184 for the paclitaxel alone arm and 173 for the paclitaxel + bevacizumab arm; see Table 14). The number of IRF-assessed progression events was higher than that used in the interim analysis conducted by ECOG's DMC in the spring of 2005 (357 vs. 260 events), even though both analyses were based on a data cutoff date of 9 February 2005. The primary reason for this difference in the number of events is the completeness of the database used. The DMC used a snapshot of the data as of 9 February 2005, which meant that the analysis was restricted to data entered in the database as of that date and did not include the complete information. For Genentech's analysis, a more complete database, including all visits up to 9 February 2005, was used, which in turn resulted in more progression events.

The results for the primary endpoint of PFS demonstrated a statistically significant and clinically meaningful increase in median PFS, from 5.8 months in the paclitaxel alone arm to 11.3 months in the paclitaxel + bevacizumab arm (see Table 14 and Figure 4). The stratified HR for the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.483 (95% CI: 0.385, 0.607; $p < 0.0001$). The unstratified analysis also demonstrated a statistically significant and clinically meaningful benefit, with a hazard ratio for the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm of 0.543 (95% CI: 0.439, 0.672; $p < 0.0001$).

Table 14
Progression-Free Survival Based on IRF Assessment:
Randomized Patients

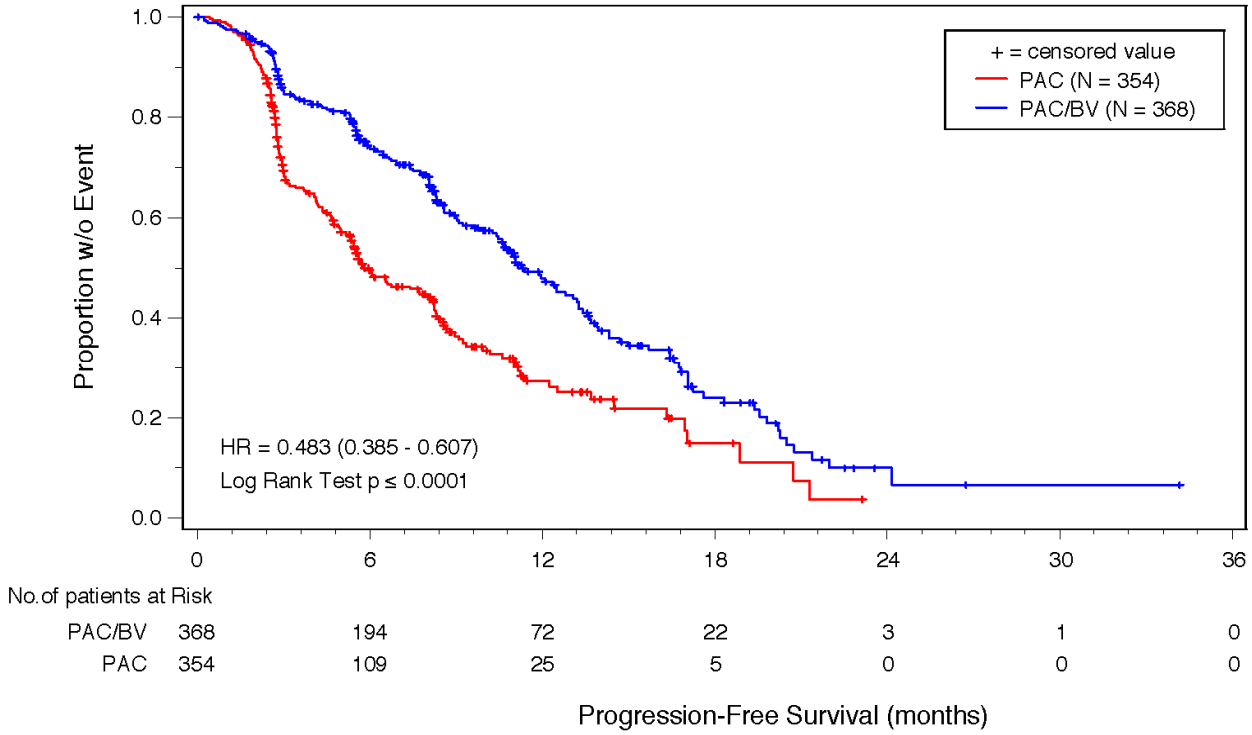
	PAC (n=354)	PAC/BV (n=368)
No. of patients	354	368
No. of patients with an event	184 (52.0%)	173 (47.0%)
Earliest contributing event		
Disease progression	166	158
On-study death [a]	18	15
Progression-free survival (months)		
Median	5.8	11.3
(95% CI)	(5.36, 8.15)	(10.45, 13.27)
25th–75th percentile	2.8–13.7	5.9–17.6
Minimum–maximum	0.0+ –23.1+	0.0+ –34.2+
Unstratified analysis		
HR (relative to PAC)	0.543	
95% CI	(0.439, 0.672)	
p-value (relative to PAC)		
Log-rank	<0.0001	
Wilcoxon	<0.0001	
Stratified analysis		
HR (relative to PAC)	0.483	
95% CI	(0.385, 0.607)	
p-value (relative to PAC)		
Log-rank	<0.0001	
Wilcoxon	<0.0001	

+=censored value; CI=confidence interval; HR=hazard ratio; IRF=independent review facility; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

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

[a] Death within 84 days of the last dose of protocol therapy.

Figure 4
Progression-Free Survival Based on IRF Assessment: Randomized Patients



HR=hazard ratio; IRF=independent review facility; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

b. Exploratory Analyses of PFS

Exploratory Analysis of PFS Based on Investigator-Reported, ECOG-Reviewed Tumor Assessments

For this exploratory analysis, Genentech applied the same analysis methods to the investigator-reported, ECOG-reviewed progression data as were applied to the IRF data.

Among the 722 randomized patients, there were 445 investigator-reported, ECOG-reviewed progression events in the two treatment arms (244 in the paclitaxel alone arm and 201 in the paclitaxel+bevacizumab arm). The results of this analysis demonstrated a statistically significant and clinically meaningful treatment effect, with median PFS of approximately 5.8 months in the paclitaxel alone arm compared with 11.4 months in the paclitaxel+bevacizumab arm, and a stratified HR of 0.421 (95% CI: 0.343, 0.516; p<0.0001).

Exploratory Analysis of PFS by Baseline Characteristics

PFS, based on IRF-assessed progression events, was analyzed with baseline characteristics and stratification factors as reported by investigators and contained in the ECOG database. Subgroups and risk factors analyzed for assessing the effect of treatment on efficacy outcomes included those defined by the four stratification variables (disease-free interval, number of metastatic sites, prior receipt of adjuvant chemotherapy, and ER status) as well as demographic and baseline characteristics, such as age ($<$40, 40–64, $\geq$65 years), race (White, non-White), baseline sum of the longest diameters of all target lesions, and HER2 expression status by fluorescent in situ hybridization and immunohistochemistry. Other characteristics considered but not pre-specified for the subgroup analysis included prior adjuvant hormonal therapy, prior hormonal therapy for locally recurrent or metastatic breast cancer, and prior taxane or anthracycline therapy.

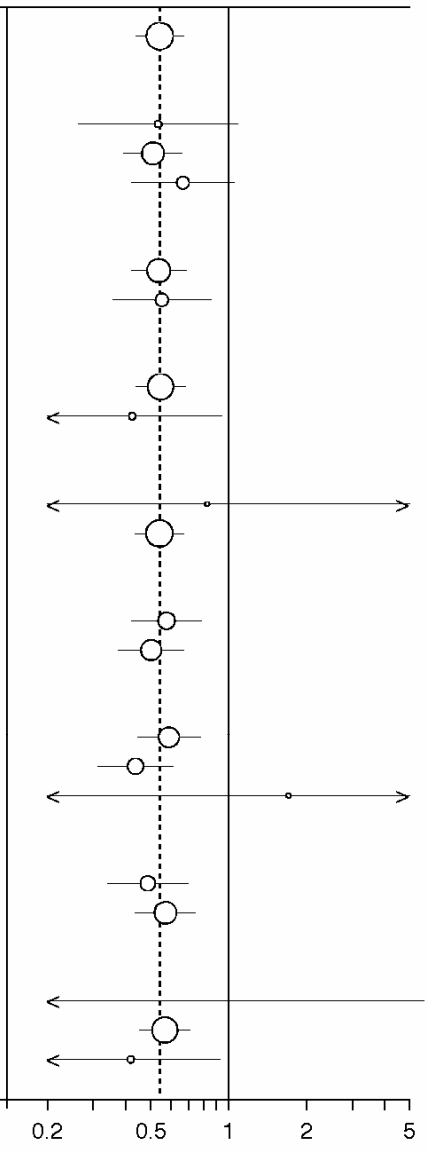
Descriptive summaries of PFS consisting of the unstratified HRs and the Kaplan–Meier estimates of median time to the event were produced for each level of the categorical variables listed above for each treatment arm. The effect of each of the baseline variables on PFS was assessed using the Cox proportional hazards model.

Reduction in the risk of IRF-assessed progression or death within clinically important patient subgroups was generally consistent with the overall treatment effect. A consistent increase in PFS was observed across all patient subgroups in the paclitaxel + bevacizumab arm (see Table 15). Patients derived PFS benefit irrespective of prior therapy (anthracyclines or taxanes), disease-free interval, disease sites, tumor burden quantified by the size of target lesions in patients with measurable disease, or hormone receptor status, including triple-negative patients (ER-, PR-, and HER2-negative).

Table 15

Progression-Free Survival by Baseline Characteristics: Randomized Patients

Baseline Risk Factor	Total n	PAC (n=354) n	PAC (n=354) Median (mo)	PAC/BV (n=368) n	PAC/BV (n=368) Median (mo)	Hazard Ratio	(95% CI)
All Patients	722	354	5.8	368	11.3	0.54	(0.44 - 0.67)
Age (yrs)							
<40	59	32	4.8	27	8.3	0.54	(0.26 - 1.09)
40-64	496	239	6.1	257	12.1	0.51	(0.39 - 0.66)
≥65	167	83	6.1	84	10.4	0.67	(0.42 - 1.05)
Race							
White	550	266	6.0	284	12.0	0.54	(0.42 - 0.69)
Non-White	172	88	5.6	84	10.9	0.55	(0.36 - 0.86)
Region							
North America	663	324	5.8	339	11.2	0.55	(0.44 - 0.68)
Rest of the World	59	30	6.5	29	12.5	0.43	(0.19 - 0.94)
Disease status							
Locally recurrent	12	4	*	8	10.9	0.83	(0.09 - 8.04)
Metastatic	709	349	5.8	360	11.4	0.54	(0.44 - 0.67)
Disease-free interval (months)							
≤24 months	296	146	4.9	150	10.6	0.58	(0.42 - 0.79)
>24 months	426	208	8.3	218	12.1	0.50	(0.38 - 0.67)
ER status							
Positive	446	223	7.7	223	11.9	0.59	(0.44 - 0.78)
Negative	265	127	4.9	138	11.1	0.44	(0.31 - 0.61)
Unknown	11	4	21.3	7	*	1.70	(0.15 - 19.07)
ER/PR/HER2 combined							
Negative	232	110	5.3	122	10.6	0.49	(0.34 - 0.70)
All others	490	244	7.4	246	12.5	0.57	(0.44 - 0.75)
HER2 status							
Positive	15	6	2.4	9	11.3	0.00	(0.00 -)
Negative	650	316	6.1	334	11.1	0.57	(0.45 - 0.71)
Unknown	57	32	7.7	25	12.5	0.42	(0.19 - 0.93)



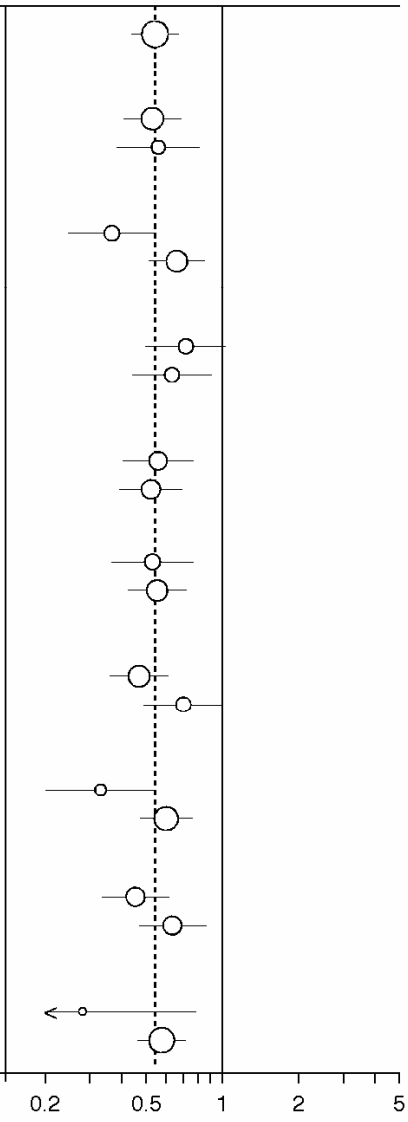
CI = confidence interval; CRF = Case Report Form; ER = estrogen receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab; PFS = progression-free survival; PR = progesterone receptor; SLD = sum of the longest diameters.

Note: Data are based on a cutoff of 9 February 2005. Values of all baseline risk factors, except SLD of target lesions and measurable disease at baseline, were based on ECOG CRFs. North America category includes the U.S. and Canada. Rest of the World category includes all other countries. HER2 was positive if amplified by FISH or 3+ by IHC per protocol. Median PFS was estimated from Kaplan–Meier curves. Hazard ratios relative to the paclitaxel alone arm were estimated by Cox regression. Unstratified hazard ratios are displayed.

Table 15 (cont'd)

Progression-Free Survival by Baseline Characteristics: Randomized Patients

Baseline Risk Factor	Total n	PAC (n=354) n	PAC (n=354) Median (mo)	PAC/BV (n=368) n	PAC/BV (n=368) Median (mo)	Hazard Ratio	(95% CI)
All Patients	722	354	5.8	368	11.3	0.54	(0.44 - 0.67)
Number of metastatic sites							
<3	514	252	6.6	262	13.3	0.53	(0.41 - 0.69)
≥3	208	102	4.8	106	8.3	0.56	(0.38 - 0.81)
Measurable disease at baseline							
No	250	111	4.1	139	16.6	0.37	(0.25 - 0.54)
Yes	472	243	6.7	229	10.7	0.66	(0.51 - 0.85)
SLD of target lesions (mm)							
≤Median (76.00)	238	116	8.6	122	11.1	0.72	(0.50 - 1.03)
>Median	234	127	5.8	107	8.6	0.63	(0.44 - 0.91)
Prior adjuvant hormone therapy							
Yes	343	175	6.1	168	12.4	0.56	(0.41 - 0.77)
No	379	179	5.5	200	11.1	0.52	(0.39 - 0.70)
Metastatic/recurrence hormone therapy							
Yes	262	128	6.0	134	11.9	0.53	(0.37 - 0.77)
No	460	226	5.8	234	11.1	0.55	(0.43 - 0.72)
Prior adjuvant chemotherapy							
Yes	475	231	5.8	244	12.4	0.47	(0.36 - 0.61)
No	247	123	6.1	124	11.2	0.70	(0.49 - 1.01)
Prior taxane therapy							
Yes	142	68	5.8	74	13.1	0.33	(0.20 - 0.54)
No	580	286	6.0	294	11.0	0.60	(0.47 - 0.76)
Prior anthracycline therapy							
Yes	364	180	6.0	184	12.8	0.46	(0.34 - 0.62)
No	358	174	5.7	184	10.6	0.64	(0.47 - 0.86)
Bone only							
Yes	63	27	8.4	36	20.5	0.28	(0.10 - 0.79)
No	658	326	5.7	332	10.9	0.58	(0.46 - 0.72)



CI=confidence interval; CRF=Case Report Form; ER=estrogen receptor; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab; PFS=progression-free survival; PR=progesterone receptor; SLD=sum of the longest diameters.

Note: Data are based on a cutoff of 9 February 2005. Values of all baseline risk factors, except SLD of target lesions and measurable disease at baseline, were based on ECOG CRFs. North America category includes the U.S. and Canada. Rest of the World category includes all other countries. HER2 was positive if amplified by FISH or 3+ by IHC per protocol. Median PFS was estimated from Kaplan–Meier curves. Hazard ratios relative to the paclitaxel alone arm were estimated by Cox regression. Unstratified hazard ratios are displayed.

c. Sensitivity Analyses for the PFS Endpoint

A number of sensitivity analyses of PFS were designed to test the robustness of the treatment effect on the primary endpoint (see Table 16).

- TTF was defined as the time from randomization to disease progression by IRF review, death from any cause, discontinuation of treatment due to toxicity, discontinuation for symptomatic deterioration, or initiation of another anti-cancer therapy. If treatment failure did not occur by the efficacy data cutoff, TTF was censored at the date reported as the patient's last tumor assessment prior to disease progression or relapse in the IRF database.

  The results for TTF (HR = 0.52; 95% CI: 0.43, 0.63) were consistent with those observed in the primary analysis, although median TTF was 4.9 and 8.3 months in the paclitaxel alone and paclitaxel + bevacizumab arms, respectively, in this analysis.

- A worst-case sensitivity analysis for the PFS endpoint was conducted. Patients in the paclitaxel + bevacizumab arm who were lost to follow-up for PFS (defined as having discontinued tumor assessments prior to progression and/or having received NPT) were considered to have had disease progression. The date of disease progression was considered to be the patient's last contact date plus 1 day. Data for patients in the paclitaxel alone arm who were lost to follow-up for PFS were censored at the date of last contact.

  The worst-case analysis (in which NPT and early discontinuation were considered progression events for patients in the paclitaxel + bevacizumab arm but were censored for patients in the paclitaxel alone arm) showed a HR of 0.78 ($p = 0.0153$).

- Another worst-case analysis, in which patients whose investigator-reported, ECOG-reviewed disease progression could not be confirmed by the IRF were considered to have had a progression event for the paclitaxel + bevacizumab arm and remained censored for the paclitaxel alone arm, showed a HR of 0.60 ($p < 0.0001$).

- A sensitivity analysis of PFS was performed that limited death events to those that occurred on or within 84 days of the last tumor assessment rather than the last protocol therapy.

- Another sensitivity analysis of PFS was performed without censoring for NPT administration.

The results of these sensitivity analyses were also generally consistent with those of the primary PFS analysis.

Table 16
Sensitivity Analyses of Progression-Free Survival

IRF-Assessed PFS Analysis	Median PFS PAC (n=354)	Median PFS PAC/BV (n=368)	HR (95% CI)
Primary analysis using 9 February 2005 cutoff date for tumor evaluation	5.8	11.3	0.48 (0.39, 0.61)
Time to treatment failure	4.9	8.3	0.52 (0.43, 0.63)
PFS analysis including deaths observed after completion of tumor assessments [a]	6.0	11.3	0.48 (0.38, 0.61)
PFS analysis without censoring for anti-tumor NPT [b]	6.1	11.2	0.57 (0.46, 0.71)
Worst-case analysis for NPT/early discontinuation [c]	5.8	8.2	0.78 (0.64, 0.95)
Worst-case analysis for missing IRF data [d]	5.8	9.2	0.60 (0.49, 0.74)

CI=confidence interval; HR=hazard ratio; IRF=independent review facility; NPT=non-protocol cancer therapy; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab; PD=progressive disease; PFS=progression-free survival.

[a] Deaths within 84 days of last tumor assessment were considered.

[b] If one or more tumor assessments were missed immediately preceding PD, the date of PD was replaced by the date of the first missed tumor assessment.

[c] In this worst-case analysis, NPT and early discontinuation were considered PD events for patients in the PAC/BV arm only.

[d] In this worst-case analysis, patients whose investigator-reported, ECOG-reviewed disease progression could not be confirmed by the IRF were considered to have had a progression event for the PAC/BV arm only.

Taken as an aggregate, both sets of sensitivity analyses of PFS demonstrated a robust and clinically significant treatment benefit for patients in the paclitaxel+bevacizumab arm.

3.2.2 Description of Missing Data

At least one scan was submitted for IRF evaluation for 649 of the 722 patients (89.9%); no scans were submitted for the remaining 73 patients (10.1%). The proportion of patients with completely missing radiographic images for the IRF review was comparable across the two treatment arms and included 35 patients (9.9%) in the paclitaxel alone arm and 38 patients (10.3%) in the paclitaxel+bevacizumab arm.

In the IRF database, 625 patients (86.6%) were evaluable and 97 patients (13.4%) were unevaluable (see Table 17). The proportion of patients with unevaluable as a best overall response was equally distributed across the two treatment arms: 50 patients (14.1%) in the paclitaxel alone arm and 47 patients (12.8%) in the paclitaxel + bevacizumab arm.

The most common reason for the assessment of unevaluable as a patient's best response was the lack of availability of scans for the retrospective IRF review. In both the IRF and ECOG databases, patients with measurable disease at baseline were distributed evenly across the two treatment arms.

Table 17
Disease Evaluability Based on IRF Data

	PAC (n = 354)	PAC/BV (n = 368)	Total (n = 722)
Evaluable	304 (85.9%)	321 (87.2%)	625 (86.6%)
Measurable disease	222 (73.0%)	218 (67.9%)	440 (70.4%)
Non-measurable disease	82 (27.0%)	103 (32.1%)	185 (29.6%)
Unevaluable	50 (14.1%)	47 (12.8%)	97 (13.4%)

IRF = Independent Review Facility; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

Similar to the IRF database, 626 patients (86.7%) were evaluable based on investigator-reported, ECOG-review tumor data, and 96 patients (13.3%) were unevaluable. The number of unevaluable patients in the ECOG database was also equally distributed across the two treatment arms: 49 patients (13.8%) in the paclitaxel alone arm and 47 patients (12.8%) in the paclitaxel + bevacizumab arm.

One of the more relevant types of missing data was a missing visit prior to an assessment that confirmed disease progression. Therefore, the IRF Charter specified that when disease progression was based on progression of a lesion that had been unevaluable at the previous timepoint, the IRF was to adjust the date of progression by moving it back to the previous timepoint. The date of disease progression was adjusted by the IRF for 53 of the 357 patients with an event in the PFS analysis (14.7%). This was balanced across the two treatment arms: 25 patients (13.6%) in the paclitaxel alone arm and 28 patients (15.9%) in the paclitaxel + bevacizumab arm.

3.2.3 Secondary Efficacy Endpoints

a. Overall Survival

Overall survival was defined as the time from randomization until death from any cause and was based on data obtained from ECOG after a complete sweep of survival data. The final analysis of overall survival was conducted after a total of 481 patients had died. This resulted in a data cutoff date of 21 October 2006, with 238 deaths in the paclitaxel alone arm and 243 deaths in the paclitaxel + bevacizumab arm.

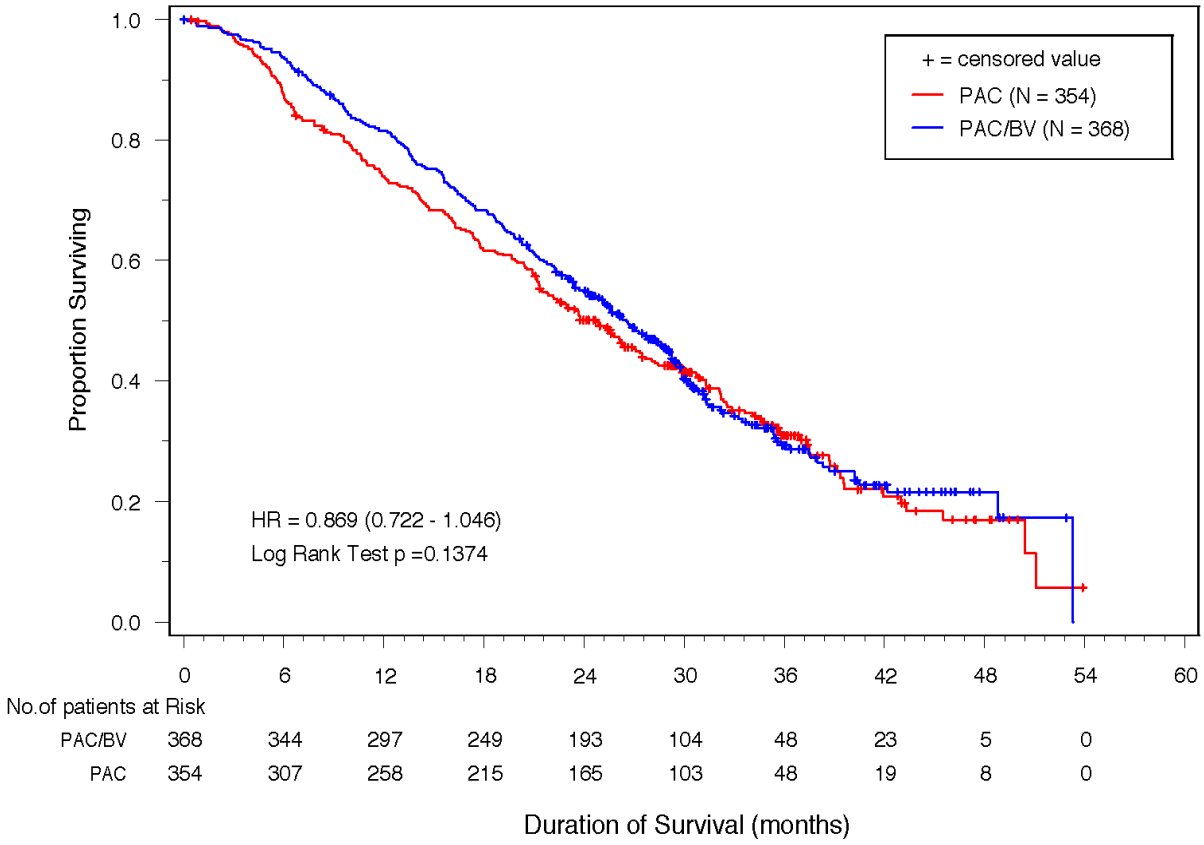
The HR for overall survival in the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.869 (95% CI: 0.722, 1.046), which corresponds to a 15% improvement in overall survival. The improvement in overall survival did not reach statistical significance ($p = 0.1374$). A 1.7-month improvement was observed in median survival, from 24.8 to 26.5 months. The Kaplan–Meier curves separated early and remained separated for well over 2 years (see Figure 5). Post-hoc landmark survival analyses demonstrated improvements in 1-year survival (74.0% vs. 81.4%; $p = 0.017$) and 2-year survival (50.1% vs. 55.0%; $p = 0.191$).

Table 18
Overall Survival: Randomized Patients

	PAC (n=354)	PAC/BV (n=368)
No. of patients	354	368
No. of patients who died	238 (67.2%)	243 (66.0%)
No. of patients not known to have died	116 (32.8%)	125 (34.0%)
Overall survival (months)		
Median	24.8	26.5
(95% CI)	(21.39, 27.37)	(23.72, 29.21)
25th–75th percentile	11.7–39.2	15.2–40.2
Minimum–maximum	0.0+ –53.9+	0.0+ –53.3
Unstratified analysis		
HR (relative to PAC)	0.932	
95% CI	(0.779, 1.114)	
p-value (relative to PAC)		
Log-rank	0.4392	
Wilcoxon	0.1744	
Stratified analysis		
HR (relative to PAC)	0.869	
95% CI	(0.722, 1.046)	
p-value		
Log-rank	0.1374	
Wilcoxon	0.0370	

+=censored value; CI=confidence interval; HR=hazard ratio; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.
Note: Data are based on a 21 October 2006 cutoff.

Figure 5
Overall Survival: Randomized Patients



HR=hazard ratio; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Exploratory Analyses for Overall Survival

More than 30 patient subgroups defined by demographics and baseline characteristics were analyzed for assessing the effect of treatment on overall survival. Comparisons of outcomes across treatment arms for these subgroups should be interpreted with caution, given that the difference in overall survival did not reach statistical significance.

Overall survival results for the subgroups were generally consistent with those observed for the entire population. An exception was the result for the age subgroups. The relatively large subgroup of patients (n=496; 69%) who were between the ages of 40 and 64 years at the time of enrollment achieved a clinically significant benefit (HR=0.77; 95% CI: 0.62, 0.96), with a nearly 5.7-month improvement in median overall survival (23.4 vs. 29.1 months).

However, patients ≥65 years of age (n=167; 23%) appeared not to benefit (HR=1.55; CI: 1.07, 2.25), with median overall survival of 27.7 and 20.7 months for the paclitaxel alone and paclitaxel+bevacizumab arms, respectively. This finding is discussed further in Section 4.2 (Risk–Benefit, by Age); the long survival (27.7 months) observed in patients ≥65 years of age who were randomized to paclitaxel alone should be noted.

b. Objective Response

Among patients with measurable disease at baseline, the IRF-assessed objective response rate was more than doubled (22.2% in the paclitaxel alone arm and 49.8% in the paclitaxel+bevacizumab arm; p<0.0001) (see Table 19). Similar results were observed among all randomized patients (15.5% in the paclitaxel alone arm and 32.3% in the paclitaxel+bevacizumab arm; p<0.0001).

Table 19
Objective Response Based on IRF Assessment: Randomized Patients with Measurable Disease at Baseline

	PAC (n=243)	PAC/BV (n=229)
No. of patients with measurable disease at baseline	243	229
No. of patients with objective response	54 (22.2%)	114 (49.8%)
Best objective response		
Complete response	0 (0.0%)	0 (0.0%)
Partial response	54 (22.2%)	114 (49.8%)
(PAC/BV−PAC)	27.6%	
95% CI	(19.2%, 35.9%)	
Stratified analysis		
p-value	<0.0001	

CI=confidence interval; IRF=independent review facility; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: Data are based on a 9 February 2005 cutoff.

Table 20 provides a summary of IRF-assessed best overall responses for patients with measurable disease at baseline.

Table 20
Best Overall Response per IRF Assessment:
Randomized Patients with Measurable Disease at Baseline

Best Overall Response	PAC (n=243)	PAC/BV (n=229)
Complete response	0 (0.0%)	0 (0.0%)
Partial response	54 (22.2%)	114 (49.8%)
Stable disease	106 (43.6%)	77 (33.6%)
Progressive disease	62 (25.5%)	27 (11.8%)
Unable to evaluate	21 (8.6%)	11 (4.8%)

IRF=independent review facility; PAC=paclitaxel;
PAC/BV=paclitaxel+bevacizumab.
Note: Data are based on a cutoff of 9 February 2005.

Subgroup analyses of IRF-assessed objective response indicated a strong and consistent benefit associated with bevacizumab+paclitaxel treatment for all subgroups examined for patients with measurable disease at baseline.

Objective response as assessed by ECOG was also doubled for all patients with measurable disease (23.4% in the paclitaxel alone arm vs. 48% in the paclitaxel+bevacizumab arm).

c. Duration of Objective Response

Among all randomized patients with an objective response as determined by the IRF, duration of objective response was approximately equal in the two treatment arms (see Table 21). Because this analysis was based on a non-randomized subset of patients, imbalances in demographics and baseline characteristics were likely; therefore, formal hypothesis testing was not performed.

Table 21
Duration of Objective Response Based on IRF Assessment: Randomized Patients with Measurable Disease at Baseline and an Objective Response

	PAC (n=54)	PAC/BV (n=114)
No. of patients with an objective response	54	112 [a]
No. of patients with an event	22 (40.7%)	56 (50.0%)
Earliest contributing event		
Disease progression	21	56
Death	1	
No. of patients without an event	32 (59.3%)	56 (50.0%)
Duration of objective response (months)		
Median	9.7	9.4
(95% CI)	(7.43, 12.62)	(8.38, 13.31)
25th–75th percentile	5.8–14.0	6.7–14.7
Minimum–maximum	2.6+ –19.4	1.9+ –25.9+

+=censored value; CI=confidence interval; IRF=independent review facility; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

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

[a] Two patients had negative durations of objective response because progressive disease was recorded prior to a partial response. These 2 patients were excluded from the duration of response analysis.

d. Agreement between ECOG-Reviewed and IRF-Based Assessments

Table 22 summarizes the results from analyses of PFS and objective response rate based on investigator-reported, ECOG-reviewed assessments and the blinded IRF assessment.

Table 22
Selected Endpoints Based on ECOG Review and IRF Assessment

	ECOG Review		IRF Assessment	
	PAC (n=354)	PAC/BV (n=368)	PAC (n=354)	PAC/BV (n=368)
PFS				
No. of patients with a PFS event	244	201	184	173
Median PFS (months)	5.8	11.4	5.8	11.3
Stratified log-rank test				
HR (95% CI)	0.421 (0.343, 0.516)		0.483 (0.385, 0.607)	
p-value	<0.0001		<0.0001	
Objective response rate [a]				
% of patients with an objective response	23.4	48.0	22.2	49.8
p-value	<0.0001		<0.0001	

CI=confidence interval; HR=hazard ratio; IRF=independent review facility; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab; PFS=progression-free survival.
[a] Based on patients with measurable disease at baseline.

As shown in Table 22, the clinically meaningful and statistically significant benefits in PFS and objective response rate with the addition of bevacizumab to paclitaxel were demonstrated by both analyses and were generally consistent between the ECOG-reviewed and IRF-based analyses.

Agreement between the IRF and ECOG assessments of PFS status was 75.9%, and disagreement between the two assessments was evenly distributed across the two treatment arms (see Table 23). Among the 548 cases for which the IRF and ECOG agreed on PFS status, there was either agreement on the date of the PFS event or a difference of <6 weeks in the date of the event for 417 cases. Differences of <6 weeks were usually attributable to minor differences in radiographic interpretation that resulted in the IRF and ECOG selecting different progression dates based on a set of examinations that constituted a single assessment period but spanned several days to a few weeks. Disagreement between the two assessments remained well balanced across the two treatment arms for this more detailed view of the data.

Table 23
Agreement between the IRF and ECOG on PFS Event Status:
Randomized Patients

Treatment Arm	Number of Disagreements	Number of Agreements
Paclitaxel alone	84 (23.7%)	270 (76.3%)
Paclitaxel + bevacizumab	90 (24.5%)	278 (75.5%)
Total	174 (24.1%)	548 (75.9%)

IRF = independent review facility; PFS = progression-free survival.

The agreement between the IRF and ECOG assessments of objective response status was 83.9% and 76.4% for the paclitaxel alone and paclitaxel + bevacizumab arms, respectively (see Table 24).

Table 24
Agreement between the IRF and ECOG on Response Status:
Randomized Patients

Treatment Arm	Number of Disagreements	Number of Agreements
Paclitaxel alone	64 (16.1%)	297 (83.9%)
Paclitaxel + bevacizumab	88 (23.6%)	280 (76.4%)
Total	152 (19.9%)	570 (80.1%)

IRF = independent review facility.

The IRF and ECOG assessment patient-level agreement rates in Study E2100 are similar to those observed in recent studies that have formed the basis for U.S. approval of other agents in MBC and other cancers (Geyer et al. 2006; M39021 Rituximab Indolent sBLA).

e. Quality of Life

The results of the secondary endpoint QOL are considered exploratory, given the open-label design, limited number of assessments, and extent of missing data.

QOL was assessed using the Functional Assessment of Cancer Therapy–Breast (FACT-B) instrument, Version 4, which consists of the following five subscales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and breast cancer–specific (BCS). The instrument was administered to patients at baseline, Week 17, and Week 33.

Each of the five subscale scores of the FACT-B, the sum PWB + FWB + BCS (Trial Outcome Index [TOI-B]; Brady et al. 1997), and the FACT-B total score was calculated for each patient at each of the three evaluations (baseline, Week 17, and Week 33).

The primary QOL analysis calculated the change from baseline for TOI-B for patients in each treatment arm (Week 17 measurement compared with baseline). When comparing TOI-B scores between groups of patients, the minimally important difference is 5–6 points (Eton et al. 2004). Missing QOL scores for patients who had progressive disease per the IRF or who died prior to Week 17 or Week 33 were replaced with 0 (i.e., the worst score). Only patients with observed values at baseline and at the indicated visit and those with imputed values were included. To explore the effect of missing data on the QOL results, sensitivity analyses were conducted using two additional imputation methods:

- For patients with missing QOL scores following death, a value of 0 (i.e., the worst score) was imputed.
- For patients with missing scores following death or disease progression, no imputation was performed.

Approximately 80% of patients were included in the primary QOL analysis. This included 70% of the population who had observed values at baseline and at Week 17 and 10% of the population who had imputed values following progression per IRF or death prior to Week 17. As seen from the negative values for the mean change in TOI-B score displayed in Table 25, QOL deteriorated in both treatment arms at Week 17 relative to baseline. Mean deterioration in QOL from baseline to Week 17 for the paclitaxel + bevacizumab arm was less than that for the paclitaxel alone arm (−6.6 vs. −12.7), and the difference in the change from baseline between the two treatment arms was statistically significant ($p = 0.0069$). Statistically significant results were also observed for Week 33. Neither sensitivity analysis for missing data showed statistically significant results at Week 17.

Table 25
Change in TOI-B from Baseline to Weeks 17 and 33:
Randomized Patients with Baseline FACT-B Assessments

	PAC			PAC/BV			
	n	Mean	SD	n	Mean	SD	p-value
Change from baseline to Week 17							
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
Change from baseline to Week 33							
Baseline	272	63.3	14.9	276	65.5	14.1	
Week 33	272	38.7	31.8	276	49.6	28.8	
Change from baseline	272	−24.6	30.5	276	−15.9	27.8	0.0002

FACT-B = Functional Assessment of Cancer Therapy–Breast; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab; QOL = quality of life; SD = standard deviation; TOI = Trial Outcome Index.

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 or Week 33 were replaced with 0 (the worst QOL score). n is the number of patients with values at baseline and at the indicated visit.

Although the effect sizes differed according to imputation methods used for missing QOL data, patients randomized to paclitaxel + bevacizumab scored higher or no differently from those randomized to paclitaxel alone in all QOL analyses, regardless of how missing data were addressed.

The results support the conclusion that there was no evidence of additional QOL burden for patients in the bevacizumab-containing arm compared with those in the paclitaxel alone arm.

3.2.4 Overall Efficacy Conclusions for Bevacizumab in Breast Cancer in Study E2100

Study E2100 was a strongly positive, multicenter, randomized, Phase III trial conducted by a highly experienced oncology cooperative group. This trial was declared positive by an independent DMC at the first interim analysis based on clearly meeting its primary endpoint. The final Genentech analysis performed for the purposes of registration demonstrated that the addition of bevacizumab to

first-line paclitaxel for patients with MBC resulted in a statistically significant and clinically meaningful improvement in PFS (HR = 0.483; $p < 0.0001$), with a 5.5-month increase in median PFS (from 5.8 to 11.3 months). This magnitude of the increase in PFS is clinically important for patients. In comparison with historical data, the paclitaxel arm performed as expected. The median PFS of 11.3 months for patients randomized to paclitaxel + bevacizumab represents the longest PFS yet reported in any first-line clinical trial in MBC and the greatest absolute improvement in PFS.

A consistent PFS benefit was observed in patient subgroups, irrespective of age, prior therapy (anthracyclines or taxanes), disease-free interval, sites of disease or tumor burden as measured by the baseline sum of the longest diameters of all target lesions, and hormone receptor status, including triple-negative patients whose tumors failed to overexpress ER, PR, or HER2. The internal consistency of the PFS results for all subgroups supports the generalizability of the overall results.

The robustness of the PFS result was further tested and verified by a variety of sensitivity analyses. All of these sensitivity analyses favored the paclitaxel + bevacizumab arm; despite the retrospective nature of the IRF review, the extent of missing data was balanced across the two treatment arms and did not appear to influence the results.

When Genentech applied the same analysis methods to the investigator-reported, ECOG-reviewed data as were applied to the IRF data, median PFS was again observed to approximately double for patients who received paclitaxel + bevacizumab compared with those who received paclitaxel alone (HR = 0.421; $p < 0.0001$), with a 5.6-month absolute increase in median PFS (from 5.8 to 11.4 months). The consistency between the PFS results based on IRF data and those based on the investigator-reported, ECOG-reviewed data observed in the Genentech analysis serves to validate the rigor of investigator assessments and the ECOG review process in this multicenter study.

Secondary endpoints included overall survival, response rate, and QOL. The HR for overall survival in the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.869 (95% CI: 0.722, 1.046), which corresponds to a

15% improvement in overall survival. The improvement in overall survival did not reach statistical significance ($p = 0.1374$). The 95% CI for the HR indicates that values between 0.722 and 1.046 are consistent with the observed data. A 1.7-month improvement was observed in median survival, from 24.8 to 26.5 months. The Kaplan–Meier curves separated early and remained separated for well over 2 years. Post-hoc landmark survival analyses demonstrated improvements in 1-year survival (74.0% vs. 81.4%; $p = 0.017$) and 2-year survival (50.1% vs. 55%; $p = 0.191$). These data provide further evidence in support of clinical benefit.

The objective response rate in patients with measurable disease at baseline as assessed by the IRF was significantly improved in the bevacizumab-containing arm (49.8% vs. 22.2%; $p < 0.0001$). Among all randomized patients with measurable disease who achieved an objective response, duration of objective response was similar across the two treatment arms: 9.7 months for the paclitaxel alone arm and 9.4 months for the paclitaxel + bevacizumab arm.

Finally, mean deterioration in QOL from baseline to Week 17 for the paclitaxel + bevacizumab arm was less than that for the paclitaxel alone arm (-6.6 vs. -12.7, respectively), and the difference in the change from baseline between the two treatment arms was statistically significant ($p = 0.0069$). There are several limitations of the QOL analyses, including the open-label nature of the study, the limited number of assessments precluding a time-to-deterioration analysis, and the relatively asymptomatic population at baseline, which makes it impossible to demonstrate an improvement in QOL over time. Finally, there is no one best way to manage the missing QOL data that result from disease progression or death. However, there was no evidence of additional QOL burden for patients in the bevacizumab-containing arm compared with those in the paclitaxel alone arm.

3.3 SAFETY RESULTS

3.3.1 Sources of Safety Data

The E2100 safety analyses presented below are based on data reported either to ECOG on the E2100 Toxicity Form (the adverse event CRF) for both treatment arms or, for patients treated with paclitaxel + bevacizumab, to NCI AdEERS for events that met the criteria for expedited reporting. Note that NCI AdEERS reports were not required for patients who received paclitaxel alone. A data cutoff date of 9 August 2005 was applied to the ECOG database, and a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

The combined database (ECOG and NCI AdEERS) was the basis for all subsequent safety analyses presented in this document. No distinction will be made between these two individual databases, unless otherwise indicated. The combined database included all Grade 3–5 non-hematologic and Grade 4 and 5 hematologic adverse events reported for both treatment arms on the E2100 Toxicity Form for non-EPP patients, regardless of causality; attributable events for the 11 treated EPP patients were included in the safety analysis.

Analyses of exposure and safety were based on patients grouped by "treatment received" or "as treated" rather than "as randomized," unless otherwise indicated.

The safety findings from previously completed bevacizumab studies, as documented in the Avastin® Package Insert, provide context for the safety findings in Study E2100 (see Appendix A). The two previously reported bevacizumab trials in patients with MBC, AVF0776g and AVF2119g, provide additional context for the evaluation of safety of bevacizumab in the treatment of women with MBC. These two breast cancer studies were included in the E2100 sBLA for evaluation of safety, per the FDA request; results are reviewed in relevant sections of this briefing document.

3.3.2 Overall Exposure

The duration of protocol therapy received was longer for patients treated with paclitaxel + bevacizumab than for those treated with paclitaxel alone, as shown by cycles and months of therapy received in Table 26. The median number of paclitaxel doses received was 17 for patients who received paclitaxel alone and

24 for those who received paclitaxel + bevacizumab. The total cumulative amount of paclitaxel (in milligrams) was substantially greater for the patients who received paclitaxel + bevacizumab than for those who received paclitaxel alone (median of 1440 mg vs. 1926 mg, respectively). However, the overall dose intensity for paclitaxel was slightly lower for patients in the paclitaxel + bevacizumab arm compared with those in the paclitaxel alone arm (85.5% vs. 95.3%, respectively); this was due to more frequent dose reductions or dose omissions in later cycles.

Table 26
Treatment Received by Cycle: Treated Non-EPP Patients

	PAC (n = 342)	PAC/BV (n = 358)
Cycles received per patient		
n	342	358
Mean (SE)	6.8 (0.3)	10.8 (0.4)
Median	6	10
Range	1–26	1–38
25th–75th percentile	3–9	6–15
Cycles received per patient		
1–3	117 (34.2%)	57 (15.9%)
4–6	89 (26.0%)	70 (19.6%)
7–9	66 (19.3%)	48 (13.4%)
10+	70 (20.5%)	183 (51.1%)
Duration of protocol therapy (months)		
n	342	358
Mean (SE)	5.9 (0.3)	9.7 (0.3)
Median	5	9
Range	0–25	0–35
25th–75th percentile	2–8	5–14

PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab; SE = standard error.
Note: A data cutoff date of 9 August 2005 was applied to the ECOG database.

3.3.3 Adverse Events

a. Treatment-Emergent Adverse Events

Overall, approximately 20% more patients treated with paclitaxel + bevacizumab reported at least one Grade 3–5 non-hematologic or Grade 4 or 5 hematologic adverse event compared with patients treated with paclitaxel alone. The large majority of the increase in adverse events was in Grade 3 events.

Events occurring at a higher incidence (≥2%) in patients treated with paclitaxel + bevacizumab versus paclitaxel alone are presented in Table 27. Events with a ≥5% higher incidence in patients treated with paclitaxel + bevacizumab versus paclitaxel alone were sensory neuropathy, hypertension, and fatigue.

The most frequently reported (≥5%) adverse events among patients treated with paclitaxel + bevacizumab were sensory neuropathy (24.2%), hypertension (16%), fatigue (10.7%), infection without neutropenia (9.1%), vomiting (5.5%), and dyspnea (5.2%), as shown in Table 28.

The most commonly reported clinically relevant Grade 4 hematologic adverse events among patients treated with paclitaxel + bevacizumab were neutropenia (reported as neutrophils) (5.8%), febrile neutropenia (0.6%), and platelet transfusion (0.3%). There were no Grade 5 hematologic adverse events (see Table 29).

Table 27

Adverse Events (Grades 3–5) by NCI-CTC Category and Term, Regardless of Causality, Occurring at a ≥2% Higher Incidence in the Paclitaxel + Bevacizumab Arm vs. the Paclitaxel Alone Arm: Treated Patients

Adverse Event Category and Term	PAC (n=348)	PAC/BV (n=363)
Any toxicity	176 (50.6%)	258 (71.1%)
Neurology	74 (21.3%)	110 (30.3%)
Neuropathy–sensory	61 (17.5%)	88 (24.2%)
Cerebrovascular ischemia	0 (0.0%)	9 (2.5%)
Cardiovascular (general)	28 (8.0%)	83 (22.9%)
Hypertension	5 (1.4%)	58 (16.0%)
Pain	33 (9.5%)	62 (17.1%)
Bone pain	6 (1.7%)	14 (3.9%)
Headache	2 (0.6%)	13 (3.6%)
Gastrointestinal	21 (6.0%)	58 (16.0%)
Vomiting	8 (2.3%)	20 (5.5%)
Diarrhea	5 (1.4%)	17 (4.7%)
Nausea	5 (1.4%)	15 (4.1%)
Dehydration	3 (0.9%)	12 (3.3%)
Infection/febrile neutropenia	20 (5.7%)	52 (14.3%)
Infection without neutropenia	16 (4.6%)	33 (9.1%)
Infection with unknown ANC	1 (0.3%)	11 (3.0%)
Constitutional symptoms	23 (6.6%)	52 (14.3%)
Fatigue	18 (5.2%)	39 (10.7%)
Metabolic/laboratory	15 (4.3%)	23 (6.3%)
Blood/bone marrow	13 (3.7%)	22 (6.1%)
Neutrophils	11 (3.2%)	21 (5.8%)
Dermatology/skin	6 (1.7%)	19 (5.2%)
Rash/desquamation	1 (0.3%)	9 (2.5%)
Renal/genitourinary	2 (0.6%)	17 (4.7%)
Proteinuria	0 (0.0%)	11 (3.0%)

ANC = absolute neutrophil count; NCI AdEERS = National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC = National Cancer Institute Common Toxicity Criteria; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

Note: This table shows NCI-CTC Grade 3–5 non-hematologic and Grade 4 and 5 hematologic adverse events, regardless of causality, that had a ≥2% difference in incidence between the two treatment arms. For 11 treated EPP patients, only possibly related adverse events were available. A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Table 28

Most Frequently Reported (≥5%) Non-Hematologic Adverse Events (Grades 3–5), by NCI-CTC Term, Regardless of Causality: Treated Patients

	PAC (n=348)			PAC/BV (n=363)		
Adverse Event Term	All Grades (3–5)	Grade 3–4	Grade 5	All Grades (3–5)	Grade 3-4	Grade 5
Neuropathy–sensory	61 (17.5%)	61 (17.5%)		88 (24.2%)	88 (24.2%)	
Hypertension	5 (1.4%)	5 (1.4%)		58 (16.0%)	58 (16.0%)	
Fatigue	18 (5.2%)	18 (5.2%)		39 (10.7%)	39 (10.7%)	
Infection without neutropenia	16 (4.6%)	16 (4.6%)		33 (9.1%)	32 (8.8%)	1 (0.3%)
Vomiting	8 (2.3%)	8 (2.3%)		20 (5.5%)	20 (5.5%)	
Dyspnea	13 (3.7%)	13 (3.7%)		19 (5.2%)	19 (5.2%)	

NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: This table shows Grade 3–5 non-hematologic adverse events, regardless of causality. For 11 treated EPP patients, only possibly related events were available. A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Table 29

Clinically Relevant Hematologic Adverse Events (Grades 4 and 5), by NCI-CTC Term, Regardless of Causality: Treated Patients

	PAC (n=348)			PAC/BV (n=363)		
Adverse Event Term	All Grades (4 and 5)	Grade 4	Grade 5	All Grades (4 and 5)	Grade 4	Grade 5
Neutrophils	11 (3.2%)	11 (3.2%)		21 (5.8%)	21 (5.8%)	
Febrile neutropenia	0 (0.0%)	0 (0.0%)		2 (0.6%)	2 (0.6%)	
Transfusion: platelets	1 (0.3%)	1 (0.3%)		1 (0.3%)	1 (0.3%)	
Platelets	2 (0.6%)	2 (0.6%)		0 (0%)	0 (0%)	

NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: This table shows clinically relevant Grade 4 and 5 hematologic adverse events, regardless of causality. For 11 treated EPP patients, only possibly related events were available. A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October was applied to the NCI AdEERS database.

b. Incidence of Grade 3–5 Non-Hematologic and Grade 4 and 5 Hematologic Adverse Events by Age and Race

Overall, patients ≥65 years of age experienced a higher incidence of adverse events and a higher incidence of each grade (Grade 3–5) of adverse events compared with the younger patients, independent of treatment arm. Consistent with what was seen in the overall study population, the incidence of adverse events was higher among patients treated with paclitaxel+bevacizumab compared with those treated with paclitaxel alone. Comparisons between these subgroups for specific types of adverse events or for events of a specific grade should be interpreted with caution given that some subgroups contained relatively small numbers of patients and the incidences of some of these toxicities were low. Thus, confidence limits would likely be wide, and patient characteristics may not be balanced across treatment arms within the subgroups. However, in assessing the effect of age and protocol therapy on specific events, an increase incidence was more apparent for patients treated with paclitaxel+bevacizumab who were ≥65 years of age than for other age groups for cerebrovascular and cardiac ischemic events (discussed below; see Grade 3–5 Arterial Thromboembolic Adverse Events), fatigue (18.5% vs.10.8%), dyspnea (8.6% vs. 4.8%), and muscle weakness (9.9% vs. 2.4%). The incidence of Grade 5 events among patients in this age group receiving paclitaxel+bevacizumab was also increased, as discussed in Section 3.3.3.c. Events that were not increased for bevacizumab-treated patients ≥65 years of age compared with patients of other age groups include sensory neuropathy and bone marrow toxicity, which may be related to the similarity in paclitaxel exposure for the two treatment arms for this age group.

Overall, White and non-White patients had similar incidences of adverse events across treatment arms. In assessing the effect of race and protocol therapy, there was an increase in the incidence of Grade 3–5 sensory (but not motor) neuropathy in non-White patients receiving paclitaxel+bevacizumab compared with non-White patients receiving paclitaxel alone. No other significant differences were seen in the non-White population. Importantly, all cases of cardiac and cerebrovascular ischemia occurred in White patients, despite an increase in stroke risk for some ethnic minorities in the general population. The increase in the incidence of events in the category of cardiac toxicity in patients treated with paclitaxel+bevacizumab was greater for White patients than for non-White

patients, although the increase in the incidence of hypertension was similar across racial groups.

c. Deaths Due to Adverse Events and Other Serious Adverse Events

Deaths

No data cutoff date was applied for the analysis of cause of death. All 511 deaths reported to ECOG prior to the data transfer to Genentech were included in analyses of safety. The causes of death, as reported by investigators, were similar across the two treatment arms, with the vast majority of deaths considered by the investigator to be due to MBC for patients in both treatment arms (see Table 30). Similarly, the majority of deaths within 30 days of the last dose of protocol therapy were considered by the investigator to be the result of MBC. One death due to protocol therapy is displayed in Table 30 (in a patient who received paclitaxel alone). In addition, Genentech's clinical review of the data identified 5 patients treated with paclitaxel + bevacizumab (1.4%) who appear to have died as the result of events that appear to have been related to protocol therapy, including deaths due to MI (2), gastrointestinal perforation (2), and cerebral ischemic event (1). Two additional paclitaxel + bevacizumab patients had sudden unexplained deaths; thus, the rate of deaths due to protocol therapy may have been as high as 1.9% (7 patients) in the paclitaxel + bevacizumab arm.

Table 30
Cause of Death, as Reported by Investigators: Treated Patients

	All Deaths		Deaths within 30 Days of Last Protocol Therapy	
	PAC (n = 348)	PAC/BV (n = 363)	PAC (n = 348)	PAC/BV (n = 363)
Total number of deaths [a]	256 (73.6%)	255 (70.2%)	7 (2.0%)	12 (3.3%)
Due to protocol therapy	1 (0.3%)	0 (0.0%) [b]	0 (0.0%)	0 (0.0%)
Due to MBC	241 (69.3%)	243 (66.9%)	4 (1.1%)	8 (2.2%)
Due to other cause	7 (2.0%)	9 (2.5%)	2 (0.6%)	4 (1.1%)
Unknown	7 (2.0%)	3 (0.8%)	1 (0.3%)	0 (0.0%)

MBC = metastatic breast cancer; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

[a] All 511 deaths were included in this table, with no data cutoff date applied to the death dataset.

[b] Based on investigator reports. Genentech clinical review resulted in a rate of 1.4%.

Table 31 presents causes of death, as reported by investigators, for patients whose death resulted from a cause other than MBC or protocol therapy.

Table 31
Cause of Death Other than Metastatic Breast Cancer

Treatment Arm/ Patient Number	Age (yr)	Cause of Death/Comments as Reported by E2100 Investigators
Paclitaxel alone arm		
21012	33	Other: *E. coli* sepsis post-craniotomy
21088	66	Due to protocol treatment; MBC; small bowel obstruction
21219	55	Unknown
21279	35	Other: patient was participating in clinical trial at Mayo (drug ixabepilone); died in hospital; unsuccessful in getting records
21284 [a]	56	Other: cardiac arrest
21287	56	Unknown
21288	74	Unknown
21409	32	Unknown
22016	72	Other: acute upper GI bleed with exsanguination and fatal shock
23003	59	Unknown
25010	57	Cause of death missing in the database; grouped in the unknown category
26024 [a]	79	Other: respiratory failure, aspiration pneumonia and hyperthyroidism (patient stopped taking thyroid med)
26030 [a]	74	Unknown: patient died at home, no autopsy done
28026	63	Other: patient went into cardiac arrest during surgery and did not recover
28063	61	Other: second primary (carcinoma of the tongue)
Paclitaxel + bevacizumab arm		
21159	77	Other: cardiac arrest
21254	59	Unknown: patient had multiple medical conditions no autopsy done/disease clinically stable upon assessment 40 days prior to death
21314 [a]	84	Other: sepsis related to ruptured diverticulum; death due to respiratory failure [b]
21390	69	Other: acute inferior MI [b]
21403 [a]	73	Other: pneumonitis; respiratory insufficiency; acute MI; CHF; death [b]
21411	69	Unknown
22025 [a]	52	Other: cardiopulmonary arrest; MBC
22038	63	Other: cardiac arrhythmia; valvular heart disease; poor ventricular function
26004 [a]	66	Other: bradycardia secondary to MBC with ascites
26028	70	Other: cerebrovascular accident [b]
28003	71	Other: probably combination of disease progression and renal failure
29009	32	Unknown; death certificate pending

CHF = congestive heart failure; GI = gastrointestinal; MBC = metastatic breast cancer; MI = myocardial infarction.
Note: No data cutoff date was applied to the death dataset.
[a] Deaths during therapy or within 30 days of the last dose of protocol therapy.
[b] Deaths ascribed to protocol therapy by Genentech clinical review.

The incidence of Grade 5 events is displayed in Table 32. Although Grade 5 events appeared to occur more frequently in patients receiving paclitaxel + bevacizumab, much of this difference is related to reports of Grade 5 constitutional symptoms. While deaths due to metastatic disease generally would not be reported to NCI AdEERS, deaths related to metastatic disease that occurred in conjunction with an event that met the reporting criteria for an NCI AdEERS report were classified by NCI as Grade 5 constitutional symptoms. Because NCI AdEERS reports were not submitted for patients who received paclitaxel alone, the observed difference in Grade 5 events could be due to reporting differences. Of the 15 patients with Grade 5 events who received paclitaxel + bevacizumab, 10 had Grade 5 events reported as constitutional symptoms and 8 of these 10 had no other confounding, life-threatening or fatal events at the time of their death. If these 8 patients had not been reported as Grade 5 events, the rate would have been identical in the two treatment arms.

The incidence of Grade 5 events in patients ≥65 years of age was also higher (at 12.3%) in the paclitaxel + bevacizumab arm than in the paclitaxel alone arm (4.8%). Much of this increase appeared to be related to deaths due to progression of breast cancer. Ten patients in this age group receiving paclitaxel + bevacizumab were reported to have had the following Grade 5 events: GI perforation (1), myocardial infarction (MI) (2), bradycardic event (1), and constitutional symptoms (6). In comparison, 4 patients in this age group who received paclitaxel alone were reported to have had the following Grade 5 events: renal failure, left ventricular dysfunction, syndrome–other, and constitutional symptoms. After constitutional symptoms were excluded, the imbalance was no longer apparent (4 vs. 3 patients).

Table 32
Grade 5 Adverse Events by NCI-CTC Category and Term Regardless of Causality: Treated Patients

Adverse Event Category and Term	PAC (n=348)	PAC/BV (n=363)
Any toxicity	7 (2.0%)	15 (4.1%)
Constitutional symptoms		
Any toxicity	3 (0.9%)	10 (2.8%)
Constitutional	3 (0.9%)	10 (2.8%)
Cardiovascular (general)		
Any toxicity	2 (0.6%)	4 (1.1%)
Cardiac–ischemia	0 (0.0%)	2 (0.6%)
Cardiac–other	1 (0.3%)	2 (0.6%)
Cardiac–left ventricular function	1 (0.3%)	0 (0.0%)
Cardiovascular (arrhythmia)		
Any toxicity	0 (0.0%)	1 (0.3%)
Sinus bradycardia	0 (0.0%)	1 (0.3%)
Gastrointestinal		
Any toxicity	0 (0.0%)	2 (0.6%)
Colitis	0 (0.0%)	1 (0.3%)
GI–other	0 (0.0%)	1 (0.3%)
Hepatic		
Any toxicity	0 (0.0%)	1 (0.3%)
Liver dysfunction/failure	0 (0.0%)	1 (0.3%)
Infection/febrile neutropenia		
Any toxicity	0 (0.0%)	1 (0.3%)
Infection w/o neutropenia	0 (0.0%)	1 (0.3%)
Pulmonary		
Any toxicity	0 (0.0%)	1 (0.3%)
Pulmonary–other	0 (0.0%)	1 (0.3%)
Renal/genitourinary		
Any toxicity	1 (0.3%)	0 (0.0%)
Renal failure	1 (0.3%)	0 (0.0%)
Syndromes		
Any toxicity	1 (0.3%)	0 (0.0%)
Syndromes–other	1 (0.3%)	0 (0.0%)

GI=gastrointestinal; NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Discontinuation of Therapy Due to Adverse Events

For patients who discontinued protocol therapy as a result of toxicity, side effects, or other complications, as reported by the investigators, the rates were similar across the two treatment arms: 19.2% among patients treated with paclitaxel alone and 20.1% among those treated with paclitaxel + bevacizumab (see Table 8). The reason for discontinuation of protocol therapy was captured once, when patients discontinued all protocol therapy. Eleven additional patients in the combination arm discontinued bevacizumab prior to progression as the result of toxicity.

Serious Adverse Events

Expedited reporting of serious adverse events was accomplished through NCI AdEERS. Among the 363 safety-evaluable patients treated with paclitaxel + bevacizumab, NCI AdEERS events were reported for 130 patients (35.8%).

Other Significant Adverse Events

The definition of adverse events of interest was based on previous bevacizumab studies and included the following categories of events: hypertension, proteinuria, arterial and venous thromboembolic events, bleeding, CHF, and GI perforation. Two types of chemotherapy-associated events—neuropathy and neutropenia/infection—are also discussed because of their known association with paclitaxel therapy.

Except for hypertension and proteinuria, each of the other adverse events of interest consisted of a list of NCI-CTC terms as determined by Genentech clinical review.

Grade 3–5 Hypertension. As expected, there was a higher incidence of Grade 3 and 4 hypertension events among patients treated with paclitaxel + bevacizumab than among those treated with paclitaxel alone, with the incidence consistent with that described in previous bevacizumab studies (see Table 33). No Grade 5 events were reported among patients treated with paclitaxel + bevacizumab, although two Grade 4 events (0.6%) were reported. No cases of reversible posterior leukoencephalopathy syndrome (RPLS) were reported in Study E2100.

These findings are similar to those reported for Study AVF2119g. The incidence of Grade 3 hypertension was 0.5% versus 20.1% in patients who received capecitabine versus capecitabine + bevacizumab, respectively; there were no cases of Grade 4 hypertension reported in Study AVF2119g.

Table 33
Grade 3–5 Hypertension: Treated Patients

Toxicity Category Term/ NCI-CTC Grade	PAC (n = 348)	PAC/BV (n = 363)
Hypertension		
Any, total	5 (1.4%)	58 (16.0%)
Grade 4	0 (0.0%)	2 (0.6%)
Grade 3	5 (1.4%)	56 (15.4%)

NCI AdEERS = National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC = National Cancer Institute Common Toxicity Criteria; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Grade 3–5 Proteinuria. As expected, there was a higher incidence of Grade 3 and 4 proteinuria among patients treated with paclitaxel + bevacizumab than among those treated with paclitaxel alone, with the incidence consistent with that described in previous bevacizumab studies (see Table 34). No Grade 5 proteinuria events were reported. These findings are similar to those reported in Study AVF2119g. The incidence of Grade 3–5 proteinuria was 0% versus 1.3% (2 Grade 3 and 1 Grade 4 events) in patients who received capecitabine versus capecitabine + bevacizumab, respectively.

Table 34
Grade 3–5 Proteinuria: Treated Patients

Toxicity Category Term/ NCI-CTC Grade	PAC (n=348)	PAC/BV (n=363)
Proteinuria		
Any, total	0 (0.0%)	11 (3.0%)
Grade 4	0 (0.0%)	4 (1.1%)
Grade 3	0 (0.0%)	7 (1.9%)

NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.
Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Grade 3–5 Arterial Thromboembolic Adverse Events. The incidence of Grade 3–5 ATE events was 3.6% among patients treated with paclitaxel+bevacizumab; no ATE events were reported among those treated with paclitaxel alone (see Table 35). Of the 13 events, 9 patients experienced a CNS event; five of these events were described as transient ischemic attacks (TIAs):

- Patient 21260 (59 years old) presented with neurologic deficits (diplopia and clumsiness) after receiving 28 cycles of bevacizumab. Her symptoms slowly resolved over 48 hours.
- Patient 21270 (66 years old) developed a TIA lasting approximately 10 minutes after receiving 3 cycles of bevacizumab.
- Patient 21393 (71 years old) presented with a TIA after beginning Cycle 5 of protocol therapy.
- Patient 22038 (63 years old) was diagnosed with a TIA after receiving 3 cycles of protocol therapy.
- Patient 28012 (67 years old) experienced a TIA in the setting of Grade 4 hypertension after receiving 14 cycles of bevacizumab.

The four cerebrovascular ATE events that were not transient are described below:

- Patient 21185 (57 years old) suffered a massive Grade 4 stroke (ischemic and hemorrhagic) approximately 4 weeks after starting Cycle 14 of protocol therapy. She died several weeks later after being transferred to a rehabilitation center.

- Patient 21243 (50 years old) developed difficulty walking, which upon evaluation was felt to be embolic strokes attributable to her underlying cancer and hypercoagulable state. She had received 30 cycles of bevacizumab prior to this event and was documented as having progressive disease within the subsequent month.
- Patient 29014 (63 years old) developed Grade 4 CNS cerebrovascular ischemia, presenting as a facial droop and expressive aphasia, after receiving 12 cycles of protocol therapy.
- Patient 29020 (77 years old) was reported to have experienced Grade 4 cerebrovascular ischemia, right homonymous hemianopsia, and Grade 3 photophobia 2 weeks after starting protocol therapy. These events occurred in association with hypertension.

Four of the 13 patients experienced a cardiac event; in two instances, the cardiac event was fatal:

- Patient 21256 (55 years old) had a Grade 4 MI associated with transient Grade 3 left ventricular dysfunction in the setting of uncontrolled hypertension approximately 8 months after the completion of protocol therapy.
- Patient 21390 (69 years old) had a fatal MI approximately 3 months after the third and last cycle of protocol therapy. Bevacizumab had been discontinued after Cycle 3 because of Grade 4 proteinuria.
- Patient 21403 (73 years old) had a Grade 5 MI and Grade 4 left ventricular dysfunction in the setting of pneumonia and respiratory insufficiency 2 weeks after initiation of protocol therapy.
- Patient 27015 (57 years old) was reported to have myocardial ischemia during Cycle 7 of protocol therapy (Grade 3), with non-specific T-wave changes and concomitant hypertension. She was also receiving rofecoxib.

Five of the 13 patients with ATE events had hypertension reported before or concurrently with their event. Six of the 13 patients were $\geq$65 years of age, including the 2 patients with fatal events.

Table 35
Grade 3–5 Arterial Thromboembolic Events: Treated Patients

Toxicity Category Term/ NCI-CTC Grade	PAC (n=348)	PAC/BV (n=363)
Patients with at least one event	0 (0.0%)	13 (3.6%)
Grade 5	0 (0.0%)	2 (0.6%)
Grade 4	0 (0.0%)	7 (1.9%)
Grade 3	0 (0.0%)	4 (1.1%)
Cerebrovascular ischemia	0 (0.0%)	9 (2.5%)
Grade 4	0 (0.0%)	6 (1.7%)
Grade 3	0 (0.0%)	3 (0.8%)
Cardiac ischemia	0 (0.0%)	4 (1.1%)
Grade 5	0 (0.0%)	2 (0.6%)
Grade 4	0 (0.0%)	1 (0.3%)
Grade 3	0 (0.0%)	1 (0.3%)

NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

The 3.6% incidence of ATE events observed in Study E2100 is consistent with the 4.4% incidence described in the Avastin® Package Insert based on 963 bevacizumab-treated patients pooled from five randomized studies. The 0.6% incidence of fatal ATE events in Study E2100 is also consistent with the 0.7% incidence reported in the Avastin® Package Insert. The increase was most apparent in patients ≥65 years of age. The incidence was 7.4% in bevacizumab-treated patients ≥65 years of age in Study E2100, which is consistent with the 8.5% incidence described for this age group in the Avastin® Package Insert.

There was no increase in the incidence of ATE events in Study AVF2119g. Two cases were reported in each treatment arm; none of the events was fatal.

Grade 3–5 Venous Thromboembolic Adverse Events. The overall incidence of Grade 3–4 venous thromboembolic events was similar across the two treatment arms (see Table 36). No Grade 5 events were reported. In Study AVF2119g,

more events occurred among patients receiving capecitabine + bevacizumab than among those receiving capecitabine alone (13 or 5.7% vs. 7 or 3.3%).

Table 36
Grade 3–5 Venous Thromboembolic Events: Treated Patients

Toxicity Category Term/ NCI-CTC Grade	PAC (n = 348)	PAC/BV (n = 363)
Thrombosis/embolism		
Any, total	15 (4.3%)	11 (3.0%)
Grade 4	7 (2.0%)	1 (0.3%)
Grade 3	8 (2.3%)	10 (2.8%)

NCI AdEERS = National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC = National Cancer Institute Common Toxicity Criteria; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Grade 3–5 Bleeding Adverse Events. Eight patients treated with paclitaxel + bevacizumab experienced a Grade 3 or 4 bleeding event, compared with 1 patient treated with paclitaxel alone (see Table 37). No Grade 5 bleeding events were reported. Of the 8 patients treated with paclitaxel + bevacizumab with bleeding events, 4 had evidence of GI tract hemorrhage. Some of these events were reported with multiple event terms applied. For example, one GI bleeding episode was reported as a duodenal ulcer, hemorrhage without Grade 3 or 4 platelets, hematemesis, and melana/GI bleeding. Another was reported as a gastric ulcer, hemorrhage without Grade 3 or 4 platelets, and melana/GI bleeding. Two of the 8 patients had CNS hemorrhages, including a Grade 4 subdural hematoma sustained after a fall and a Grade 4 CNS hemorrhage associated with concomitant warfarin use in the setting of a Grade 4 cerebrovascular ischemic event. The remaining 2 patients had Grade 3 epistaxis and Grade 3 hematuria in the setting of thrombocytopenia. Four of the 8 patients with Grade 3 or 4 bleeding events were ≥ 65 years of age.

In Study AVF2119g, 1 Grade 3 bleeding event was reported in each treatment arm.

Table 37
Grade 3–5 Bleeding Events: Treated Patients

Toxicity Category Term/NCI-CTC Grade	PAC (n=348)	PAC/BV (n=363)
Patients with at least one event	1 (0.3%)	8 (2.2%)
Grade 5	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	2 (0.6%)
Grade 3	1 (0.3%)	6 (1.7%)
Grade 3 hemorrhage without Grade 3 or 4 platelet	0 (0.0%)	2 (0.6%)
Grade 3 melena/GI bleeding	1 (0.3%)	3 (0.8%)
Grade 4 CNS hemorrhage	0 (0.0%)	2 (0.6%)
Grade 3 epistaxis	0 (0.0%)	1 (0.3%)
Grade 3 hematemesis	1 (0.3%)	2 (0.6%)
Grade 3 hemorrhage–other	0 (0.0%)	1 (0.3%)
Grade 3 hematuria	0 (0.0%)	1 (0.3%)

NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Grade 3–5 Congestive Heart Failure. The incidence of Grade 3–5 left ventricular dysfunction events, using NCI-CTC v2.0, was 2.2% in patients receiving paclitaxel+bevacizumab compared with 0.3% in those receiving paclitaxel alone (see Table 38). One Grade 5 event was reported, and that event occurred in a patient who received paclitaxel alone. Seven of the 8 patients treated with paclitaxel+bevacizumab who experienced Grade 3 or 4 left ventricular dysfunction had previously received anthracycline therapy. Among those who had received prior anthracycline therapy, the incidence of Grade 3 and 4 left ventricular dysfunction was 3.8%, which is consistent with the incidence described in the Avastin® Package Insert for patients who have previously received anthracycline therapy. Hypertension, a known risk factor for CHF, was reported as an adverse event for 2 of these patients during the course of the study. Preexisting hypertension was not captured. Age is also a known risk factor for CHF; however, only 1 of the 8 patients treated with paclitaxel+bevacizumab who developed CHF was ≥65 years of age. The patient

treated with paclitaxel alone who experienced the fatal event was ≥65 years of age at study entry. She had reportedly received no prior anthracycline-based chemotherapy.

Table 38
Grade 3–5 Left Ventricular Dysfunction Events: Treated Patients

Toxicity Category Term/ NCI-CTC Grade	PAC (n=348)	PAC/BV (n=363)
Left ventricular function		
Any, total	1 (0.3%)	8 (2.2%)
Grade 5	1 (0.3%)	0 (0.0%)
Grade 4	0 (0.0%)	1 (0.3%)
Grade 3	0 (0.0%)	7 (1.9%)

NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.
Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

The incidence of Grade 3 and 4 CHF events reported in Study AVF2119g for patients who received capecitabine+bevacizumab was 3.5%, compared with 1% for those who received capecitabine alone. All patients had received prior anthracycline therapy; their median prior cumulative doxorubicin dose was 240 mg/m^2 (range: 240–360 mg/m^2). In addition, of these 8 patients, 4 had received radiotherapy to the left chest wall.

Gastrointestinal Perforation. GI perforation is an expected but infrequently observed potential adverse event associated with bevacizumab therapy. GI perforation was reported for 2 patients (0.6%) treated with paclitaxel+bevacizumab; both events were fatal (see Table 39). Death occurred within 36 and 15 days of onset of the two events. One patient was 64 years old; the other patient was 84 years old. No identified GI perforation events were reported in patients treated with paclitaxel alone.

Intra-abdominal abscess and fistula adverse events may be complications associated with occult GI perforation. No intra-abdominal abscesses were reported in either treatment arm, although 1 additional patient treated with

paclitaxel + bevacizumab, not included in Table 39, developed a Grade 4 rectal/anal fistula that required a colostomy.

Table 39
Selected Grade 3–5 Gastrointestinal Perforations: Treated Patients

Toxicity Category Term/ NCI-CTC Grade	PAC (n = 348)	PAC/BV (n = 363)
GI perforation		
Any, total	0 (0.0%)	2 (0.6%)
Grade 5	0 (0.0%)	2 (0.6%)
Grade 4	0 (0.0%)	0 (0.0%)

NCI AdEERS = National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC = National Cancer Institute Common Toxicity Criteria; PAC = paclitaxel; PAC/BV = paclitaxel + bevacizumab.

Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Grade 3–5 Sensory or Motor Neuropathy Events. There was a modestly higher incidence of Grade 3 neuropathy events in patients treated with paclitaxel + bevacizumab compared with those treated with paclitaxel alone. No Grade 5 events were reported, and only 2 patients in each treatment arm experienced a Grade 4 event; all Grade 4 events were sensory neuropathy and not motor neuropathy.

The higher incidence of neuropathy reflects, in large part, the greater time on therapy; patients in the paclitaxel alone arm received a median of 6 cycles of protocol therapy (and 1440 mg of paclitaxel) compared with 10 cycles (and 1926 mg of paclitaxel) for those in the paclitaxel + bevacizumab arm. As a result, there was a longer duration of adverse event reporting. After adjusting for duration of adverse event reporting, the incidence of Grade 3 and 4 neuropathy was similar across the two treatment arms. The observation time–adjusted incidence rate per 100 patient-years was also similar for the two treatments arms (33.18 for the paclitaxel alone arm vs. 32.34 for the paclitaxel + bevacizumab arm).

There was no report of Grade ≥ 3 neuropathy in Study AVF2119g.

Table 40
Grade 3–5 Sensory and Motor Neuropathy: Treated Patients

Toxicity Category Term/ NCI-CTC Grade	PAC (n=348)	PAC/BV (n=363)
Neuropathy		
Any, total	63 (18.1%)	92 (25.3%)
Grade 4	2 (0.6%)	2 (0.6%)
Grade 3	61 (17.5%)	90 (24.8%)
Neuropathy–sensory		
Any, total	61 (17.5%)	88 (24.2%)
Grade 4	2 (0.6%)	2 (0.6%)
Grade 3	59 (17.0%)	86 (23.7%)
Neuropathy–motor		
Any, total	6 (1.7%)	11 (3.0%)
Grade 3	6 (1.7%)	11 (3.0%)

NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

Prior taxane exposure did not appear to increase the risk of developing neuropathy, nor did age. In patients ≥65 years of age, the incidence of neuropathy was similar across the two treatment arms. In contrast to the exposure data for the entire population, the median number of paclitaxel doses administered in this age group was similar for the two treatment arms (17 doses for patients who received paclitaxel and 18 doses for those who received paclitaxel+bevacizumab).

In summary, patients in Study E2100 who received paclitaxel+bevacizumab had a higher incidence of Grade 3 sensory and motor neuropathy than those who received paclitaxel alone. After adjusting for duration of adverse event reporting, the incidence was similar across the two treatment arms. This, along with the absence of sensory neuropathy in Study AVF2119g, suggests that the neuropathic complications were not intrinsic to bevacizumab therapy but to the chemotherapy concomitantly administered, which is consistent with the knowledge that the incidence and severity of sensory neuropathy increase with

cumulative paclitaxel exposure (Lipton et al. 1989; Perez et al. 2001; Mielke et al. 2005).

Neutropenia/Infection. Grade 3–5 infections required reporting to ECOG, whereas only Grade 4 and 5 neutropenia events required reporting. As displayed in Table 29, there was no increase in Grade 4 or 5 clinically relevant hematologic adverse events. There was an increase in the incidence of Grade 3 infection events among patients treated with paclitaxel + bevacizumab compared with those treated with paclitaxel alone; however, this analysis was not adjusted for time on treatment (see Table 41). There was also no clear increase observed in Grade 4 or 5 events, although the only Grade 5 event (an infection without neutropenia) did occur in a patient who received paclitaxel + bevacizumab. One Grade 4 febrile neutropenia event was reported in a patient who received paclitaxel + bevacizumab, and one Grade 4 infection associated with neutropenia occurred in a patient who received paclitaxel alone.

No significant increase in the incidence of neutropenia or infection was observed in Study AVF2119g.

Table 41

Grade 3–5 Neutropenia/Infection Events: Treated Patients

Toxicity Category Term/ NCI-CTC Grade	PAC (n=348)	PAC/BV (n=363)
Neutropenia and/or infection		
Any, total	28 (8.0%)	63 (17.4%)
Grade 5	0 (0.0%)	1 (0.3%)
Grade 4	12 (3.4%)	22 (6.1%)
Grade 3	16 (4.6%)	40 (11.0%)
Infection without neutropenia		
Any, total	16 (4.6%)	33 (9.1%)
Grade 5	0 (0.0%)	1 (0.3%)
Grade 3	16 (4.6%)	32 (8.8%)
Neutrophils		
Any, total	11 (3.2%)	21 (5.8%)
Grade 4	11 (3.2%)	21 (5.8%)
Infection with Grade 3 or 4 neutropenia		
Any, total	5 (1.4%)	10 (2.8%)
Grade 4	1 (0.3%)	0 (0.0%)
Grade 3	4 (1.1%)	10 (2.8%)
Infection with unknown ANC		
Any, total	1 (0.3%)	11 (3.0%)
Grade 3	1 (0.3%)	11 (3.0%)
Febrile neutropenia		
Any, total	0 (0.0%)	5 (1.4%)
Grade 4	0 (0.0%)	2 (0.6%)
Grade 3	0 (0.0%)	3 (0.8%)
Infection–other		
Any, total	0 (0.0%)	4 (1.1%)
Grade 4	0 (0.0%)	1 (0.3%)
Grade 3	0 (0.0%)	3 (0.8%)
Catheter-related infection		
Any, total	0 (0.0%)	3 (0.8%)
Grade 3	0 (0.0%)	3 (0.8%)

NCI AdEERS=National Cancer Institute Adverse Event Expedited Reporting System; ANC=absolute neutrophil count; NCI-CTC=National Cancer Institute Common Toxicity Criteria; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Note: A data cutoff date of 9 August 2005 was applied to the ECOG database; a data cutoff date of 30 October 2006 was applied to the NCI AdEERS database.

The dose and schedule of paclitaxel selected for Study E2100 was not significantly myelosuppressive, as evidenced by a relatively modest incidence of these events in patients receiving weekly paclitaxel alone. Bevacizumab has been observed to increase the incidence of neutropenia and infection when administered with myelosuppressive chemotherapy in other clinical trials. Patients in Study E2100 who received paclitaxel + bevacizumab experienced a higher incidence of Grade 3 infection/febrile neutropenia than those who received paclitaxel alone. However, the patients treated with paclitaxel + bevacizumab who developed neutropenia or infection received significantly more paclitaxel (median of 35 doses) than those who did not develop neutropenia or infection (median of 21 doses). Because there are data to suggest that VEGF is important in recovery of bone marrow progenitor cells following chemotherapy, bevacizumab therapy alone is unlikely to have contributed to the increase in rates of severe myelosuppression. Finally, the overall increase in neutropenia and infection events was not associated with an increase in life-threatening events such as sepsis in Study E2100.

3.3.4 Overall Safety Conclusions for Bevacizumab in Breast Cancer

The safety conclusions can be summarized as follows:

- Overall, no new safety signals were noted with the addition of bevacizumab to first-line paclitaxel therapy for patients with locally recurrent or metastatic breast cancer relative to events identified in the Avastin® Package Insert.
- The incidence of Grade 3 and 4 adverse events was increased by approximately 20% in patients treated with paclitaxel + bevacizumab (71.1%) compared with those treated with paclitaxel alone (50.6%).

  Nearly all of this increase was in the incidence of Grade 3 events, mainly hypertension and neuropathy. The latter may, in large part, reflect the greater time on therapy; patients in the paclitaxel alone arm received a median of 6 cycles of protocol therapy (and 1440 mg of paclitaxel) compared with 10 cycles (and 1926 mg of paclitaxel) for those in the paclitaxel + bevacizumab arm. As a result, there was a longer duration of adverse event reporting. The incidence of Grade 3 sensory neuropathy was comparable between treatment arms after adjusting for the greater observational time in the paclitaxel + bevacizumab arm.

  Grade 3 and 4 adverse events that were increased by ≥5% in patients treated with paclitaxel + bevacizumab compared with those treated with paclitaxel alone were sensory neuropathy (24.2% vs. 17.5%),

hypertension (16.0% vs. 1.4%), and fatigue (10.7% vs. 5.2%). Other categories of events, when combined, also showed increases of ≥5%, although no individual toxicity within these categories was increased to the same degree. These include the categories of pain events (17.1% vs. 9.5%), GI toxicity (16.0% vs. 6.0%), and infection and febrile neutropenia (14.3% vs. 5.7%).

- With regard to age subgroups, the safety profile for patients ≥65 of age who received paclitaxel + bevacizumab appeared to be similar to the profile for younger patients, with a few notable exceptions.

  ATE events were more frequent among patients ≥65 years of age in the paclitaxel + bevacizumab arm (at 7.4%) compared with patients ≥65 years of age in the paclitaxel alone arm (0%) and bevacizumab-treated younger patients (2.7% in patients 40–64 years of age and 0% in those <40 years of age). The relationship between age and risk of a bevacizumab-associated ATE event has been previously described, and the rate observed in bevacizumab-treated patients ≥65 years of age in Study E2100 was consistent with the 8.5% incidence described for this age group in the Avastin® Package Insert.

  The rate of bleeding events was also more frequent in patients ≥65 years of age who received paclitaxel + bevacizumab (4.9% vs. 0%).

- No clinically significant factors appeared to be related to race when toxicity rates in White patients were compared with those in non-White patients by treatment arm.

- The incidences of events that have previously been associated with bevacizumab, including Grade 3–5 hypertension, left ventricular dysfunction, proteinuria, bleeding, GI perforation, and ATE events, were increased, but were within the range of expected toxicity, both in terms of incidence and severity.

  Several of these events were considered manageable or were generally asymptomatic and did not detract from the overall clinical benefit achieved when bevacizumab was added to weekly paclitaxel.

  Clinically, the most serious bevacizumab-associated toxicity observed in this trial was ATE; the incidence of ATE events was within the range expected based on data contained in the Avastin® Package Insert.

  The risk of left ventricular dysfunction was not increased above that described in studies of patients with previously treated MBC. Prior anthracycline exposure appeared to be a contributing factor.

The incidences of Grade 3–5 adverse events of special interest for the paclitaxel + bevacizumab arm in Study E2100 were as follows:

Grade 3–5 hypertension, 16.0% (Grade 5, 0%)

Grade 3–5 proteinuria, 3.0% (Grade 5, 0%)

Grade 3–5 ATE events, 3.6% (Grade 5, 0.6%)

Grade 3–5 venous thromboembolic events, 3.0% (Grade 5, 0%)

Grade 3–5 bleeding events, 2.2% (Grade 5, 0%)

Grade 3–5 CHF, 2.2% (Grade 5, 0%)

GI perforation events, 0.6% (Grade 5, 0.6%)

Grade 3–5 neuropathy events, 25.3% (Grade 5, 0%)

Neutropenia/infection (multiple categories of events combined), 17.4% (Grade 5, 0.3%)

The incidences of the above reported events are similar to those described in the Avastin® Package Insert (provided in Appendix A).

4. RISK–BENEFIT DISCUSSION

4.1 RISK–BENEFIT IN THE OVERALL POPULATION

The results of Study E2100 demonstrate that bevacizumab provided a consistent and clinically significant benefit when added to paclitaxel for the treatment of advanced breast cancer, translating into a favorable risk–benefit profile for the overall population.

- Study E2100 demonstrated a statistically significant and clinically meaningful improvement in PFS (HR = 0.483; $p < 0.0001$), with a 5.5-month increase in median PFS (from 5.8 to 11.3 months).
- A consistent PFS benefit was observed in patient subgroups irrespective of age and other baseline factors.
- The HR for overall survival in the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.869 (95% CI: 0.722, 1.046), which corresponds to a 15% improvement in overall survival. The improvement in overall survival did not reach statistical significance ($p = 0.1374$).

  Post-hoc landmark survival analyses demonstrated improvements in 1-year survival (74.0% vs. 81.4%; $p = 0.017$) and 2-year survival (50.1% vs. 55.0%; $p = 0.191$).
- The objective response rate in patients with measurable disease at baseline as assessed by the IRF was significantly improved in the bevacizumab-containing arm (49.8% vs. 22.2%; $p < 0.0001$).
- There was no evidence of additional QOL burden for patients in the bevacizumab-containing arm compared with the paclitaxel alone arm
- Overall, the safety profile of bevacizumab when combined with paclitaxel in this population is consistent with that observed in previous studies of bevacizumab plus chemotherapy in patients with MBC, as well as that seen in other tumor types.

4.2 RISK–BENEFIT, BY AGE

Although a favorable risk–benefit profile was observed overall and in nearly all subgroups evaluated, the risk–benefit profile in patients ≥65 years of age merits additional discussion.

- In the exploratory subset analysis of PFS, the observed HR for patients ≥65 years of age was 0.67 (95% CI: 0.42, 1.05) in favor of the paclitaxel + bevacizumab arm, with a corresponding 4.3-month improvement in median PFS (from 6.1 to 10.4 months).

- In the exploratory subset analysis of objective response rate, an improvement in objective response rate was observed for patients ≥65 years of age with measurable disease (19.0% to 37.3%) with the addition of bevacizumab.
- In the exploratory subset analysis of overall survival, the observed HR for patients ≥65 years of age was 1.55 (95% CI: 1.07, 2.25), suggesting a negative treatment effect.

  Within this subgroup, the Kaplan–Meier curves did not begin to separate until after 12 months. The median duration of therapy was 6 months for patients in this age group. In addition, the median survival of 27.7 months in patients randomized to paclitaxel alone was notably better than expected, whereas the median survival of 20.7 months for patients randomized to paclitaxel + bevacizumab appears to be more consistent with expectations. Whether this observation is indicative of a true treatment detriment or was due to chance (more than 30 subgroups were evaluated), a limited sample size (117 deaths observed in the subgroup), an imbalance in baseline characteristics or other unmeasured factors, or possible differences in subsequently received active treatments, is unknown.
- The safety profile of bevacizumab in patients ≥65 years of age was consistent with the established profile in patients ≥65 years of age observed in previous Phase III studies in other tumor types.

  The 7.4% incidence of ATE events observed in patients ≥65 years of age in Study E2100 was consistent with the 8.5% incidence previously described for this age group in other bevacizumab trials. Although the incidence of bleeding was 4.9% in this age group in the study, none of these events were fatal.
- Treatment-related mortality did not explain the observed HR of 1.55 in the exploratory subset analysis of overall survival.

  The Grade 5 events in this population receiving paclitaxel + bevacizumab included one GI perforation, two fatal MIs, and one bradycardic event, plus 6 patients who died of MBC reported as Grade 5 constitutional symptoms. In comparison, 4 patients in this age group who received paclitaxel alone were reported to have had the following Grade 5 events: renal failure, left ventricular dysfunction, syndrome–other, and constitutional symptoms. After constitutional symptoms were excluded for the paclitaxel + bevacizumab arm and after clinical review of details for individual patients for both treatment arms, the incidence of fatal toxicities was similar across the two treatment arms.

Based on the findings describe above, definitive conclusions regarding the benefits and risks for patients ≥65 years of age are more difficult to draw based on data from Study E2100 alone.

To further understand this result, overall survival is presented in Table 42 for patients ≥65 years of age enrolled in Study E2100, Study AVF2119g, and the randomized, Phase III studies that led to FDA approvals for Avastin® (colorectal cancer and non–small cell lung cancer). With the exception of Study AVF2119g, which did not meet the primary endpoint of PFS or the secondary endpoint of overall survival, the other studies all met their primary endpoint of overall survival with prospectively specified subgroup analyses for age.

Table 42
Overall Survival in Patients ≥65 Years of Age in Selected Bevacizumab Phase III Studies

			Non–Bevacizumab-Containing Regimen		Bevacizumab-Containing Regimen		
Study	Disease Setting	Total N (Age ≥65 yr)	n	Median (mo)	n	Median (mo)	HR (95% CI)
E2100	1st line MBC	167	83	27.7	84	20.7	1.55 (1.07, 2.25)
AVF2119g [a]	≥2nd line MBC	53	31	16.46	22	12.11	1.00 (0.54, 1.88)
AVF2107g	1st line mCRC	271	141	14.92	130	24.15	0.61 (0.43, 0.87)
E3200	2nd line mCRC	217	106	10.1	111	12.5	0.80 (0.60, 1.06)
E4599	1st line mNSCLC	379	194	11.7	185	11.3	0.91 (0.72, 1.14)

CI=confidence interval; HR=hazard ratio; mCRC=metastatic colorectal cancer; MBC=metastatic breast cancer; mNSCLC=metastatic non–small cell lung cancer.

[a] Data based on the AVF2119g Clinical Study Report Addendum were used because only 19 deaths had been observed at the time of the data cutoff for the Clinical Study Report (the median had not been reached for either treatment arm).

Although the number of patients ≥65 years of age was small in most of these studies, the HRs of 0.61 to 1.00 observed in these studies provide reassurance that bevacizumab does not harm the survival of older patients in general.

5. OVERALL CONCLUSIONS

Study E2100 was a strongly positive, multicenter, randomized, Phase III trial conducted by a preeminent U.S. oncology cooperative group. This trial was declared positive by the independent DMC at the first interim analysis based on clearly meeting its primary endpoint. Blinded, independent review validated these findings in the subsequent analyses conducted by Genentech.
The robustness of the treatment benefit, as measured by PFS, was further demonstrated by the consistent benefit in all subgroups examined and by extensive sensitivity analyses. In total, the data demonstrate a highly favorable risk–benefit profile for bevacizumab in combination with paclitaxel. In the following discussion, we attempt to place the safety and efficacy results of Study E2100 in the broader context of the regulatory environment.

Evidence from all study endpoints supports the conclusion that patients who received bevacizumab in addition to paclitaxel derived clinical benefit.
The magnitude of the effect of adding bevacizumab to paclitaxel and the impact on PFS are statistically very persuasive (5.5-month improvement in the median; HR = 0.483; $p < 0.0001$). The median PFS among patients in the paclitaxel + bevacizumab arm (11.3 months) represents a high mark when compared with the paclitaxel alone arm (5.8 months) of Study E2100 and with historical trials, in which PFS of the experimental arm has ranged from 4 to 9 months. The paclitaxel alone arm behaved as expected with respect to both the PFS and overall survival endpoints. The improvement in PFS was consistent across all patient subgroups irrespective of age or other baseline factors.

The more than doubling of the objective response rate (from 22.2% to 49.8%; $p < 0.0001$) indicates that the addition of bevacizumab to paclitaxel did more than just delay progression. The HR for overall survival in the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm (HR = 0.869; 95% CI: 0.722, 1.046) corresponds to a 15% improvement in overall survival. The improvement did not reach statistical significance ($p = 0.1374$), but the 95% CI for the HR indicates that values between 0.722 and 1.046 are consistent with the observed data. The Kaplan–Meier curves separated early and remained separated for well over 2 years, and post-hoc landmark survival analyses demonstrated improvements in 1-year survival (74.0% vs. 81.4%; $p = 0.017$) and 2-year survival (50.1% vs. 55%; $p = 0.191$). These data provide further evidence

in support of clinical benefit. Finally, there is no evidence of additional QOL burden for patients in the bevacizumab-containing arm compared with those in the paclitaxel alone arm. In summary, the results of Study E2100 provide evidence of the highly meaningful clinical effectiveness of bevacizumab in combination with paclitaxel for the treatment of patients who have not received chemotherapy for locally recurrent or metastatic breast cancer.

Examination of the efficacy data from Study E2100 indicates that the criteria contained in the FDA Guidance with regard to effect size, effect duration, and benefit compared with other available therapies (see Section 1.1.4) have been met. In addition, maintaining disease control can delay symptomatic decline of patients at or following disease progression—again supporting the relevancy of PFS as a measure of benefit.

Per the FDA Guidance, an evaluation for bias or uncertainty regarding tumor endpoint assessments must also be considered when deciding whether PFS is acceptable for accelerated versus full approval. Independent confirmation of the primary endpoint by a committee blinded to treatment is noted to be important, and essential in open-label trials.

The rigorous IRF assessment of the primary endpoint by a blinded, central IRF indicates that any bias entering into the trial as the result of the open-label design did not impact the conduct of the study or the assessment of the primary endpoint of PFS. The IRF assessment of progression not only demonstrated statistically persuasive findings of improved PFS ($HR = 0.483$; $p < 0.0001$), but also served to validate the rigorous conduct of the study since the IRF assessment was consistent with PFS based on the investigator-reported, ECOG-reviewed tumor data. This consistency supports the robustness of the cooperative group processes for assessing tumor response and progression. Even though the IRF review was conducted retrospectively, scan collection efforts were robust, and there was no evidence that missing data affected the outcome of the study. The robustness of the PFS result was demonstrated by a variety of sensitivity analyses; benefit was maintained even in two worst-case analyses. Therefore, examination of the data from Study E2100 indicates that the criteria delineated by the FDA regarding approval based on PFS have been met and that the PFS endpoint in Study E2100 may serve as the basis for full approval.

No new safety signals were identified, and none of the known bevacizumab-associated events occurred at an incidence higher than what had previously been reported. Weekly paclitaxel is a very well-tolerated regimen; toxicity of the regimen when bevacizumab was added to weekly paclitaxel did not detract from the overall clinical benefit achieved. Therefore, the risk–benefit profile in the overall population is favorable.

In summary, the results from Study E2100 support the conclusion that bevacizumab provides a consistent and clinically significant benefit when added to paclitaxel in the first-line treatment of patients with MBC. Bevacizumab, in combination with paclitaxel, provides a significant advance in the treatment of MBC, compelling efficacy, and an acceptable safety profile. We believe that Avastin® should receive full approval for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer.

6. REFERENCES

A'Hern RP, Smith IE, Ebbs SR. Chemotherapy and survival in advanced breast cancer: the inclusion of doxorubicin in Cooper type regimens. Br J Cancer 1993;67:801–5.

Alba E, Ruiz-Borrego M, Martín M, et al. Prolongation of TTP by maintenance therapy with PLD in a multicenter phase III randomized trial following standard chemotherapy for MBC: GEICAM 2001-01 study. J Clin Oncol 2007;25(20 June Suppl):1007.

American Cancer Society, Inc. Estimated cancer deaths for selected sites by state, US, 2007. [table on the Internet]. Available from: http://www.cancer.org/downloads/stt/CFF2007EstDthSelSiteByState.pdf.

Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 multicenter Phase III trial. J Clin Oncol 2002;20:3114–21.

Bontenbal M, Creemers G-J, Braun HJ, et al. Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch community setting trial for the Clinical Trial Group of the Comprehensive Cancer Centre. J Clin Oncol 2205;23:7081–8.

Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy – Breast quality-of life instrument. J Clin Oncol 1997;15:974–86.

Chan S, Romieu G, Huober J, et al. Gemcitabine plus docetaxel (GD) versus capecitabine plus docetaxel (CD) for anthracycline-pretreated metastatic breast cancer (MBC) patients (pts): results of a European phase III study [abstract]. J Clin Oncol 2005;23(1 June Suppl):581.

Chia SK, Speers CH, D'yachkova Y, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. Cancer 2007;110:973–9.

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007. http://www.fda.gov/cber/gdlns/clintrialend.htm

Coates A, Gebski V, Bishop JF, et al. Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies. N Engl J Med 1987;317:1490–5.

Cobleigh MA, Langmuir VK, Sledge GW, et al. A Phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol 2003;30(Suppl 16):117–24.

Escudier B, Koralewski P, Pluzanska A, et al., on behalf of the AVOREN Investigators. A randomized, controlled, double-blind Phase III study (AVOREN) of bevacizumab/interferon-α2a vs placebo/interferon-α2a as first-line therapy in metastatic renal cell carcinoma [abstract]. J Clin Oncol 2007;25(June 20 Suppl):3.

Eton DT, Cella D, Yost KJ, et al. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol 2004;57:898–910.

Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocr Rev 1997;18:4–25.

Folkman J. What is the evidence that tumors are angiogenesis dependent? J Nat Cancer Inst 1990a;82:4–6.

Folkman J. Endothelial cells and angiogenic growth factors in cancer growth and metastasis. Introduction. Cancer Metastasis Rev 1990b;9:171–4.

Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1995;1:27–31.

Folkman J. Antiangiogenic therapy. In: DeVita VT Jr, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology, fifth edition. Philadelphia: Lippincott-Raven, 1997:3075–85.

Fossati R, Confalonieri C, Torri V, et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J Clin Oncol 1998;16:3439–60.

Gennari A, Amadori D, De Lena M, et al. Lack of benefit of maintenance paclitaxel in first-line chemotherapy in metastatic breast cancer. J Clin Oncol 2006;24:3912–8.

Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733–43.

Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539–44.

Hamilton A, Hortobagyi G. Chemotherapy: what progress in the last 5 years? J Clin Oncol 2005;23:1760–75.

Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.

Jassem J, Pienkowski T, Pluzanska A, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized Phase III multicenter trial. J Clin Oncol 2001;19:1707–15.

Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 2003;21:1404–11.

Jones SE, Erban J, Overmoyer B, et al. Randomized Phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005;23:5542–51.

Kindler HL, Niedzwiecki D, Hollis D, et al. A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): a preliminary analysis of Cancer and Leukemia Group B (CALGB) [abstract]. J Clin Oncol 2007;25(June 20 Suppl):4508.

Lipton RB, Apfel SC, Dutcher JP, et al. Taxol produces a predominantly sensory neuropathy. Neurology 1989;39:368–73.

Lueck H, Minckwitz GV, Du Bois A, et al. Epirubicin/paclitaxel (EP) vs. capecitabine/paclitaxel (XP) in first-line metastatic breast cancer (MBC): a prospective, randomized multicentre Phase III study of the AGO breast cancer study group. J Clin Oncol 2006;24(June 20 Suppl):517.

Luo J, Guo P, Matsuda K, et al. Pancreatic cancer cell-derived vascular endothelial growth factor is biologically active in vitro and enhances tumorigenicity in vivo. Int J Cancer 2001;92:361–9.

Melemed AS, O'Shaughnessy J, Nag S, et al. Phase III study of gemcitabine plus paclitaxel compared with paclitaxel alone in patients with unresectable, locally recurrent, or metastatic breast cancer [abstract]. J Clin Oncol 2007 Breast Cancer Symposium. Abstract 150.

Mielke S, Sparreboom A, Steinberg SM, et al. Association of paclitaxel pharmacokinetics with the development of peripheral neuropathy in patients with advanced cancer. Clin Cancer Res 2005;11:4843–50.

Miller K, Wang M, Gralow J, et al. E2100: a randomized Phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Proceedings of the 41st American Society of Clinical Oncology Annual Meeting; 2005a May 13–17:Orlando (FL).

Miller KD, Chap LI, Holmes FA, et al. Randomized Phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005b;23:792–9.

Muñoz M, Martín M, Ruiz A, et al. Phase III study of gemcitabine plus vinorelbine (VG) versus vinorelbine (V) in patients (pts) with metastatic breast cancer (MBC) previously treated with anthracyclines (A) and taxanes (T). Final results of GEICAM 2000–04 study. J Clin Oncol 2006;24(June 20 Suppl):575.

Nabholtz J-M, Falkson C, Campos D, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, Phase III trial. J Clin Oncol 2003;21:968–75.

National Comprehensive Cancer Network (NCCN) Guidelines in Oncology. Breast Cancer v.2.2007 http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J Clin Oncol 2002;20:2812–23.

Perez EA, Vogel CL, Irwin DH, et al. Multicenter Phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 2001;19:4216–23.

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

Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 2006;355:2542–50 [erratum 2007;356:318].

Seidman AD, Berry D, Cirrincione C, et al. CALGB 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour (h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC [abstract]. J Clin Oncol 2004;22(July 15 Suppl):512.

Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an Intergroup trial (E1193). J Clin Oncol 2003;21:588–92.

Smith I. Goals of treatment for patients with metastatic breast cancer. Semin Oncol 2006;33(1 Suppl 2):S2–5.

Stockler M, Sourijina T, Grimison P, et al. A randomized trial of capecitabine (C) given intermittently (IC) rather than concomitantly (CC) compared to classical CMF as first-line chemotherapy for advanced breast cancer (ABC). J Clin Oncol 2007;25(June 20 Suppl):1031.

Vahdat LT, Thomas E, Li R, et al. Phase III trial of ixabepilone plus capecitabine compared to capecitabine alone in patients with metastatic breast cancer (MBC) previously treated or resistant to an anthracycline and resistant to taxanes. J Clin Oncol 2007;25(June 20 Suppl):1006.

Verrill MW, Lee J, Cameron DA, et al. Anglo-Celtic IV: first results of a UK National Cancer Research Network randomised Phase 3 pharmacogenetic trial of weekly versus 3 weekly Paclitaxel in patients with locally advanced or metastatic breast cancer (ABC) [abstract]. J CLin Oncol 2007;25(June 20 Suppl):LBA1005.

von Marschall Z, Cramer T, Hocker M, et al. De novo expression of vascular endothelial growth factor in human pancreatic cancer: evidence for an autocrine mitogenic loop. Gastroenterology 2000;119:1358–72.

Weidner N, Semple JP, Welch WR, et al. Tumor angiogenesis and metastasis—correlation in invasive breast carcinoma. N Engl J Med 1991;324:1–8.

Weidner N, Folkman J, Pozza F, et al. Tumor angiogenesis: a new significant and independent prognostic indicator in early-stage breast carcinoma. J Natl Cancer Inst 1992;84:1875–87.

Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003;349:427–34.

Zielinski C, Beslija S, Mrsic-Krmpotic Z, et al. Gemcitabine, epirubicin, and paclitaxel versus fluorouracil, epirubicin, and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: a Central European cooperative oncology group international, multicenter, prospective, randomized Phase III trial. J Clin Oncol 2005;23:1401–8.

7. APPENDICES

Appendix A: Avastin® Package Insert

APPENDIX A
Avastin® Package Insert

1.14.2.3 Final Labeling Text

AVASTIN®
(Bevacizumab)

For Intravenous Use

WARNINGS

Gastrointestinal Perforations

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

Wound Healing Complications

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

Hemorrhage

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

DESCRIPTION

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

CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacokinetics

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

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

Special Populations

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

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

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

CLINICAL STUDIES

AVASTIN® in Metastatic Colorectal Cancer (mCRC)

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

AVASTIN in Combination with Bolus-IFL

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

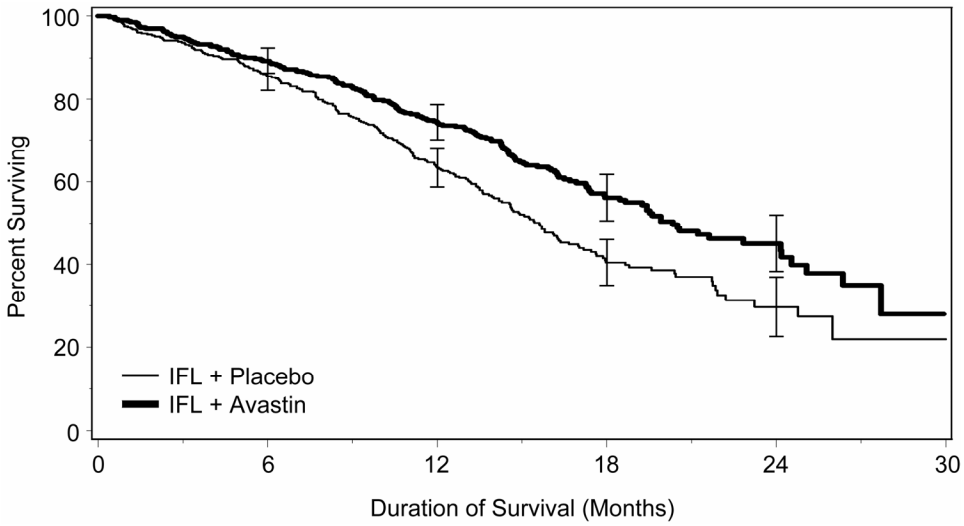
Of the 813 patients randomized to Arms 1 and 2, the median age was 60, 40% were female, and 79% were Caucasian. Fifty-seven percent had an ECOG performance status of 0. Twenty-one percent had a rectal primary and 28% received prior adjuvant chemotherapy. In the majority of patients, 56%, the dominant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

Table 1
Study 1 Efficacy Results

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

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

Figure 1
Duration of Survival in Study 1



Error bars represent 95% confidence intervals.

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

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

AVASTIN in Combination with 5-FU/LV Chemotherapy

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

Table 2
Study 2 Efficacy Results

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

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

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

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

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

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

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

AVASTIN in Third-Line Metastatic Colorectal Cancer

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

There was one objective partial response in the first 100 evaluable patients for an overall response rate of 1% (95% CI 05.5%).

AVASTIN® in Unresectable Non–Squamous, Non–Small Cell Lung Cancer (NSCLC)

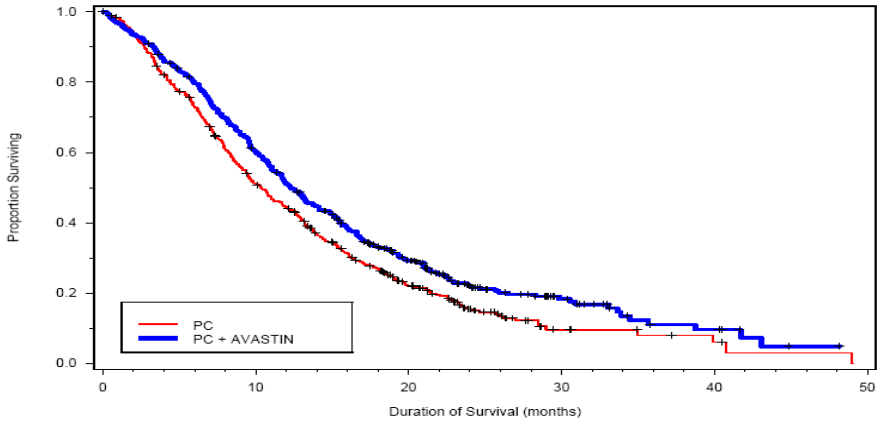
The safety and efficacy of AVASTIN as first-line treatment of patients with locally advanced, metastatic, or recurrent non-squamous, NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study (Study 5, n=878), supported by a randomized, dose ranging, active controlled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

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

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

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

Figure 2
Duration of Survival in Study 5



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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None.

WARNINGS

Gastrointestinal Perforations

(See DOSAGE AND ADMINISTRATION: Dose Modifications)

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

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

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

Non–Gastrointestinal Fistula Formation

(See DOSAGE AND ADMINISTRATION: Dose Modifications)

Non–gastrointestinal fistula formation has been reported in patients treated with AVASTIN in controlled clinical studies (with an incidence of <0.3%)

and in post-marketing experience, in some cases with fatal outcome. Fistula formation involving the following areas of the body other than the gastrointestinal tract have been reported: tracheo-esophageal, bronchopleural, biliary, vagina and bladder. Events were reported throughout treatment with Avastin, with most events occurring within the first 6 months.

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

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

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

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

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

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

Hemorrhage

(See DOSAGE AND ADMINISTRATION: Dose Modifications)

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

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

The risk of central nervous system (CNS) bleeding in patients with CNS metastases receiving AVASTIN has not been evaluated because these patients were excluded from late stage clinical studies following

development of CNS hemorrhage in a patient with a CNS metastasis in a Phase 1 study.

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

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

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

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

The safety of resumption of AVASTIN therapy after resolution of an ATE has not been studied. Permanently discontinue AVASTIN in patients who experience a severe ATE during treatment. (See **DOSAGE AND**

ADMINISTRATION: Dose Modifications and **PRECAUTIONS: Geriatric Use**.)

Hypertension
(See DOSAGE AND ADMINISTRATION: Dose Modifications)

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

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

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

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

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

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

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

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

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

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

Proteinuria
(See DOSAGE AND ADMINISTRATION: Dose Modifications)

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

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

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

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

Congestive Heart Failure

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

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

PRECAUTIONS

General

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

Infusion Reactions

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

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

Surgery

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

Cardiovascular Disease

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

Laboratory Tests

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

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

Drug Interactions

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Pregnancy Category C

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

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

Nursing Mothers

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

Pediatric Use

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

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

Geriatric Use

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

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

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

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

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

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

ADVERSE REACTIONS

The most serious adverse reactions in patients receiving AVASTIN were:

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

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

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

Adverse Reactions in Clinical Trials

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

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

Gastrointestinal Perforation

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

Non–Gastrointestinal Fistula Formation

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

Wound Healing Complications

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

Hemorrhage

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

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

Arterial Thromboembolic Events

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

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

Venous Thromboembolic Events

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

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

Hypertension

Fatal CNS hemorrhage complicating AVASTIN induced hypertension can occur.

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

Table 3
Incidence of Hypertension and Severe Hypertension in Study 1

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

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

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

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

Neutropenia and Infection

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

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

Proteinuria

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

Immunogenicity

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

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

Metastatic Carcinoma of the Colon and Rectum

The data in Table 4 and Table 5 were obtained in Study 1. All NCI-CTC Grade 3 and 4 adverse events and selected NCI-CTC Grade 1 and 2 adverse events (hypertension, proteinuria, thromboembolic events) were

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

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

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

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

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

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

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

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

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

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

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

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

Non–Squamous, Non–Small Cell Lung Cancer

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

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

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

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

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

Other Serious Adverse Events

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

Body as a Whole: polyserositis

Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic ulceration

Hemic and lymphatic: pancytopenia

Respiratory: nasal septum perforation

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Metastatic Carcinoma of the Colon or Rectum

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

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

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

Non–Squamous, Non–Small Cell Lung Cancer

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

Dose Modifications

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

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

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

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

Preparation for Administration

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

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

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

Administration

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

Stability and Storage

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

HOW SUPPLIED

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

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

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

REFERENCES

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

AVASTIN®
(Bevacizumab)

For Intravenous Use

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

7455311
LV0017
4835702
Initial U.S.Approval: February 2004
Code Revision Date: September 2007