BRIEFING BOOK

ONCOLOGY DRUGS
ADVISORY COMMITTEE MEETING

AVASTIN® (Bevacizumab)

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BRIEFING BOOK
AVASTIN® (Bevacizumab)

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1. EXECUTIVE SUMMARY

Breast cancer is the most common cancer in women worldwide. It is estimated that more than 40,000 women in the United States died of metastatic breast cancer (MBC) in 2009 (American Cancer Society 2009). When breast cancer has metastasized, it is incurable, with over 90% of patients ultimately dying from the disease. Although several chemotherapeutic agents have been approved as first-line treatment for patients with MBC, use of the most active agents for early-stage disease can limit patients' options in the metastatic setting.

On 22 February 2008, Avastin® (bevacizumab), in combination with paclitaxel, was granted accelerated approval for the treatment of women who had not received chemotherapy (first-line) for HER2-negative MBC based on the results of the Phase III trial E2100. Under the accelerated approval mechanism (21 CFR §601.40–46), the United States Food and Drug Administration (FDA) can approve products for cancer or other life-threatening diseases on the basis of initial positive data showing clinical evidence of a favorable benefit–risk assessment.

In accordance with the FDA approval letter (provided in Appendix A), Genentech is addressing requirements to further define the degree of clinical benefit and convert the accelerated approval to full approval. On 16 November 2009, Genentech submitted two supplemental Biologics License Applications (sBLAs) based on two additional Phase III trials, AVADO (BO17708) and RIBBON1 (AVF3694g). Prior to submission, the FDA provided guidance indicating that these data would need to demonstrate improvement in progression-free survival (PFS) and provide evidence that overall survival was not impaired when Avastin was combined with chemotherapy.

On the basis of data from AVADO and RIBBON1 and the accelerated approval conditions outlined by the FDA, Genentech is requesting conversion from accelerated approval to full approval for Avastin in combination with paclitaxel and expansion of the label to include use of Avastin in combination with other chemotherapies, including taxane-based, anthracycline-based, and capecitabine chemotherapy, for the first-line treatment of patients with HER2-negative MBC.

The full approval of Avastin and the expansion of the indication to allow Avastin to be combined with several chemotherapies will provide physicians more information on the safety and efficacy profile of Avastin in combination with commonly used and clinically relevant chemotherapeutic agents other than paclitaxel, and will allow them greater flexibility in tailoring treatment decisions to the needs of individual patients.

The combined evidence from E2100, AVADO, and RIBBON1 outlined in this briefing book clearly demonstrates that Avastin in combination with standard chemotherapy regimens is safe and effective for the first-line treatment of women with HER2-negative MBC.

Consistent and Reliable Improvement in Progression-Free Survival

E2100, AVADO, and RIBBON1 were international, multicenter, randomized, well-conducted, Phase III trials:

- E2100, an open-label, controlled trial of 722 patients randomized 1:1 to Avastin + paclitaxel or paclitaxel alone, was the basis of the accelerated approval.
- AVADO was a double-blind, placebo-controlled, three-arm trial of 736 patients randomized 1:1:1 to docetaxel + placebo, docetaxel + Avastin 7.5 mg/kg, or docetaxel + Avastin 15 mg/kg.
- RIBBON1 was a double-blind, placebo-controlled trial of Avastin plus either taxane-based, anthracycline-based, or capecitabine chemotherapy versus chemotherapy alone. Patients were randomized 2:1 to chemotherapy + Avastin 15 mg/kg or chemotherapy + placebo. This study consisted of two independently powered comparisons under a single protocol: the taxane/anthracycline-based chemotherapy comparison (622 patients) and the capecitabine comparison (615 patients).

E2100, AVADO, and RIBBON1 were designed with the primary objective of showing that combining Avastin with standard chemotherapy regimens significantly improved PFS. PFS was chosen because it represents the time that a woman's disease remains under control and directly measures the effect of the current treatment. Overall survival was a secondary endpoint in all three studies. It has become increasingly challenging in clinical trials to measure the effect of first-line treatments for patients with MBC on overall survival, as patients are living longer and it is difficult to control the treatments administered after a clinical trial (see Section 2.1).

All three Phase III trials demonstrated that Avastin in combination with commonly used chemotherapies provided a consistent, reliable, and statistically significant improvement in PFS, the time women lived with HER2-negative MBC under control. Across the studies, treatment with Avastin combined with standard chemotherapy regimens decreased a woman's risk of disease progression or death by 31% to 52%. Additional results from these studies provided further evidence of meaningful clinical benefit to patients:

- Improvements in PFS were seen across all prognostic categories and patient subgroups, including age, extent of metastasis at study entry, and hormone receptor status.
- The rate of objective responses (a measure of tumor shrinkage) was 11.8% to 27.6% higher for Avastin-treated women than those treated with chemotherapy alone.

While extending the time women lived with HER2-negative MBC under control, treatment with Avastin in combination with standard chemotherapy regimens did not adversely affect women's self-reported quality of life more than chemotherapy alone.

Avastin in Combination with Chemotherapy Did Not Impair Overall Survival

Comprehensive analyses from all three studies demonstrated that the combination of Avastin with chemotherapy did not impair overall survival:

- Overall survival was not different between treatment arms (hazard ratios [HRs] ranged from 0.87 to 1.11 across studies, with overlapping confidence intervals).
- There was no increase in treatment-related deaths or deaths overall in women treated with Avastin plus chemotherapy versus chemotherapy alone. Additionally, results from a pooled analysis demonstrated no difference between treatment arms in overall survival (stratified HR = 0.97; 95% CI: 0.86, 1.08). Together, these results indicate that treatment with Avastin in combination with first-line chemotherapy did not impair overall survival.

A Safety Profile Consistent with Previous Experience across Different Cancers and the Avastin® U.S. Package Insert

Together, E2100, AVADO, and RIBBON1 enrolled nearly 2700 women, and in all three studies, Avastin was well tolerated. The safety profile observed in these studies was generally consistent with the well-established profile observed in the more than 812,000 patients treated with Avastin worldwide,

in multiple cancer types, and as described in the currently approved Avastin® U.S. Package Insert:

- The incidence of common adverse events associated with Avastin treatment (e.g., hypertension and proteinuria) was consistent with reports from previous studies; these are events that are not associated with symptoms and are managed through routine clinical interventions.
- The incidence of severe safety events known to be associated with the combination of Avastin and chemotherapy (e.g., arterial thromboembolic events, gastrointestinal perforation, and severe bleeding) was low (<4%).
- The combination of Avastin with chemotherapy did not substantially increase the incidence of adverse events typically associated with the background chemotherapy, such as neutropenia or sensory neuropathy with taxane therapy.
- There was no increase in treatment-related deaths or deaths overall, and no specific adverse event was associated with treatment-related deaths.

Substantial Evidence Supporting Avastin as an Important Treatment for Patients with MBC

Data from the three Phase III trials outlined in this briefing book show that combining Avastin with commonly used first-line chemotherapies significantly improved PFS, increased objective response rates, and did not impair overall survival. The combination of Avastin and chemotherapy was well tolerated, and the safety profile of Avastin in this setting was consistent with extensive previous experience.

Data from AVADO and RIBBON1 support conversion of the accelerated approval to full approval based on FDA-agreed upon criteria for the following indication:

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

These results also support expansion of the Avastin® label to include the following indication:

> Avastin, in combination with taxane-based, anthracycline-based, or capecitabine chemotherapy, is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

A full approval and broadened indication will provide physicians and patients more treatment choices for keeping this incurable disease under control.

2. INTRODUCTION

The United States Food and Drug Administration (FDA) has granted accelerated approval for Avastin® (bevacizumab), in combination with paclitaxel, for the treatment of patients who have not received chemotherapy for their HER2-negative metastatic breast cancer (MBC). Under the accelerated approval mechanism, the FDA can approve products for cancer or other life-threatening diseases on the basis of initial positive clinical data. The approval was based on a Phase III trial (E2100) which showed that treatment with Avastin in combination with paclitaxel resulted in a prolongation of progression-free survival (PFS) (based on a hazard ratio [HR] of 0.48; $p < 0.0001$), equivalent to a 52% reduction in the risk of disease progression or death compared with paclitaxel alone. The safety profile of Avastin was consistent with previous Avastin experience, and no new safety signals were observed.

In accordance with the FDA approval letter (see Appendix A), Genentech is addressing requirements to further define the degree of clinical benefit and convert the accelerated approval to full approval by submission of two supplemental Biologics License Applications (sBLAs) based on the results of two additional Phase III trials (AVADO and RIBBON1).

This briefing book summarizes the safety and efficacy data from these three clinical trials of Avastin with chemotherapy for the treatment of patients who have not received chemotherapy for HER2-negative MBC (first-line treatment). Genentech believes that these data represent substantial evidence of clinical benefit supporting the following:

- Conversion to full approval for the indication in combination with paclitaxel based on criteria agreed upon with the FDA to further define the degree of clinical benefit

  Submission of data from two additional Phase III trials, AVADO and RIBBON1 (demonstration that PFS is improved and overall survival is not impaired)

- Expansion of the Avastin label to include the following indication

  Avastin, in combination with taxane-based, anthracycline-based, or capecitabine chemotherapy, is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

The results from the primary analyses of all studies consistently demonstrated that Avastin in combination with taxane-based, anthracycline-based, and capecitabine chemotherapy provided meaningful clinical benefit, as measured by PFS. This benefit was demonstrated across a broad study population, which included patients with poor prognostic features (e.g., triple-negative disease, visceral disease, and short disease-free interval). The substantial evidence generated from these large randomized clinical trials indicates that Avastin, given in combination with standard chemotherapy regimens, is an important advance in the treatment of patients with previously untreated HER2-negative MBC.

2.1 METASTATIC BREAST CANCER

Breast cancer is the most commonly occurring cancer in women worldwide. It is a heterogeneous disease that is classified by specific molecular, pathologic, and clinical features, which can have prognostic and predictive value (Chang et al. 2003; Slamon et al. 1987; Weidner et al. 1991, 1992). Intrinsic patient factors, such as co-morbidity and age, and anatomical sites of disease, also determine the clinical course and outcome for patients.

When breast cancer has metastasized, it becomes incurable, with over 90% of patients ultimately dying from their disease. The goals of MBC treatment are to achieve disease control (i.e., durable tumor response, stabilization of disease, or improvements in PFS), to palliate symptoms, and to prolong survival while maintaining quality of life.

Treatment options for patients with MBC are expanding and include the use of single-agent or combination chemotherapy, hormonal therapy, and targeted biologic therapy. The decision-making process involved in choosing a patient's treatment course is complex and requires tailoring based on tumor-related symptoms, tumor burden, competing medical co-morbidities, age, and treatment-induced toxicities that are acceptable for individual patients. With new diagnostic and therapeutic advances, the overall life expectancy of patients has improved, despite the lack of evidence demonstrating the specific advantage of any single treatment over another.

Patients whose tumors overexpress HER2 are candidates for HER2-targeted therapies. (Note: HER2-positive MBC was not evaluated in the clinical trials described in this briefing book.) Patient's whose tumors are hormone receptor

(estrogen and/or progesterone receptor) positive are candidates for endocrine therapy, provided their disease is localized to bone or soft tissue, or they do not require immediate response to control visceral metastasis. No targeted therapies are currently available specifically for patients whose tumors are negative for both hormone receptors and for HER2 (specifically studied in the Avastin trials and referred to as triple-negative breast cancer), representing a breast cancer patient population for whom there is an unmet medical need.

Patients with symptomatic or life-threatening visceral metastases and those whose disease is refractory to hormonal therapy should be treated with cytotoxic chemotherapy. The extent and location of metastatic disease can influence whether cytotoxic chemotherapy is given as monotherapy, as a chemotherapy doublet, or in combination with targeted therapies. Ultimately, treatment decisions are influenced by prognostic factors as well as a balance between physician and individual patient preferences and expectations with regards to the efficacy and toxicity of the treatment options. The decision-making process involves both physician and patient perspectives throughout the course of the disease (Hayes 2009)

Similar to the disease, the regulatory landscape for MBC drug approval is complex and has evolved over the last 30 years. Drugs approved in the 1970s for the treatment of patients with MBC were primarily cytotoxic drugs (alkaloids, anti-metabolites, anti-folates, and anthracyclines) and tamoxifen, and approvals were granted on the basis of tumor response. Additional drug approvals were infrequent until the 1990s, when a greater understanding of tumor biology led to a proliferation of targeted drug development for MBC. Consequently, the FDA approved a number of drugs for MBC between 1994 and 2010. FDA drug approval from 1977 to 2010 are summarized in Table 1.

Table 1
Summary of Agents Approved for the Treatment of Patients with Metastatic Breast Cancer (1977–2010)

Therapies for Hormone Receptor–Positive Disease	First-Line Therapy for MBC			Second- or Third-Line Therapy
	HER2-Positive	HER2-Negative	Not Restricted to HER2 Status	
Anastrozole (1995, 2000)	Trastuzumab (with paclitaxel) (1998)	Avastin (with paclitaxel) [a] (2008)	Docetaxel [a] (1996)	Capecitabine [a] (1998)
Exemestane (1999)	Lapatinib (with letrozole) [a] (2010)		Nab-paclitaxel (2005)	Capecitabine (with docetaxel) [b] (2001)
Fulvestrant (2002)			Paclitaxel (1994)	Docetaxel [b] (1996, 1998)
Goserelin (1995)			Gemcitabine (with paclitaxel) (2004)	Ixabepilone (2007)
Letrozole (1997, 2001)				Lapatinib (with capecitabine) (2007)
Tamoxifen (1977, 1989, 1993, 2005)				Paclitaxel (1994)
Toremifene (1997)				Trastuzumab (1998)

[a] Accelerated approval.

[b] Accelerated approval converted to full approval.

The threshold of evidence required by the FDA to support full approval is dependent on the patient population and disease setting, as well as the agent's mechanism of action. Endocrine therapies (estrogen receptor modulators and aromatase inhibitors) have been approved for the treatment of patients with hormone-sensitive disease on the basis of tumor response (response rate), time to disease progression (TTP), and PFS. Tumor response is a direct measure of the drug's effect (tumors rarely shrink without treatment), while PFS represents an important measure of disease control and a clinically relevant delay before new treatment needs to be initiated. Because hormonal agents have somewhat moderate toxicity profiles, the assessment of benefit–risk for these agents is more favorable than that for cytotoxic chemotherapy. Therefore, survival data have not been required for approval of hormonal agents.

For cytotoxic and biologic agents, full FDA approvals in the first-line MBC setting have been based on TTP or PFS, with supportive survival data (e.g., docetaxel, paclitaxel, trastuzumab, and gemcitabine). Approvals in second- and third-line MBC settings

have also been based primarily on TTP or PFS data (e.g., paclitaxel, docetaxel, and capecitabine).

The National Comprehensive Cancer Network (NCCN) guidelines (V.2.2010) detail the treatment strategy and therapeutic options for patients with MBC based on widely recognized prognostic and predictive factors (Chang et al. 2003). The agents listed in the NCCN guidelines may or may not have been approved by the FDA for the specific recommended use, but may be viewed as generally consistent with the FDA-approved package inserts and labeled indications. These guidelines (summarized in Table 2) are based on peer-reviewed evidence and consensus of the NCCN authors regarding views of currently accepted approaches to breast cancer treatment.

Table 2
Adapted from the NCCN Guidelines (V.2.2010):
Preferred Chemotherapy Regimens for Recurrent
or Metastatic HER2-Negative Breast Cancer

Preferred Single Agents	Preferred Combinations (Chemotherapy + Chemotherapy or Chemotherapy + Biologic)
Doxorubicin	CAF and FAC
Epirubicin	FEC
Pegylated liposomal doxorubicin	AC
Paclitaxel	EC
Docetaxel	AT
Albumin-bound paclitaxel	CMF
Capecitabine	Docetaxel + gemcitabine
Gemcitabine	Gemcitabine + paclitaxel
Vinorelbine	Paclitaxel + Avastin (bevacizumab)

AC = doxorubicin + cyclophosphamide; AT = doxorubicin + paclitaxel;
CAF = cyclophosphamide + doxorubicin + 5-fluorouracil;
CMF = cyclophosphamide + methotrexate + 5-fluorouracil;
EC = epirubicin + cyclophosphamide;
FAC = 5-fluorouracil + doxorubicin + cyclophosphamide;
FEC = 5-fluorouracil + epirubicin + cyclophosphamide.

The list of available therapies appears to be extensive; however, patients' options can be limited in the metastatic disease setting because of the use of adjuvant treatment regimens containing the most active agents (anthracyclines and taxanes).

Metastatic disease may acquire some resistance to drugs administered as adjuvant therapy, and the toxicities associated with these agents may preclude their continued use in the metastatic setting (Gonzales-Angulo et al. 2007).

A number of randomized, Phase III trials conducted in the last decade in the first-line MBC setting have used PFS or TTP to objectively measure drug or regimen efficacy. These endpoints are not confounded by subsequent treatment and, for cytostatic drugs, assess disease control in addition to tumor response. Median PFS or TTP observed in these randomized trials of chemotherapy for HER2-negative MBC ranges from 4 to 12 months. For studies demonstrating an improvement in PFS or TTP, hazard ratios in favor of the experimental arm range from 0.54 to 0.73 (see Table 3).

Table 3
Summary of Recent Trials of Chemotherapeutic Agents for the First-Line Treatment of Patients with HER2-Negative Metastatic Breast Cancer

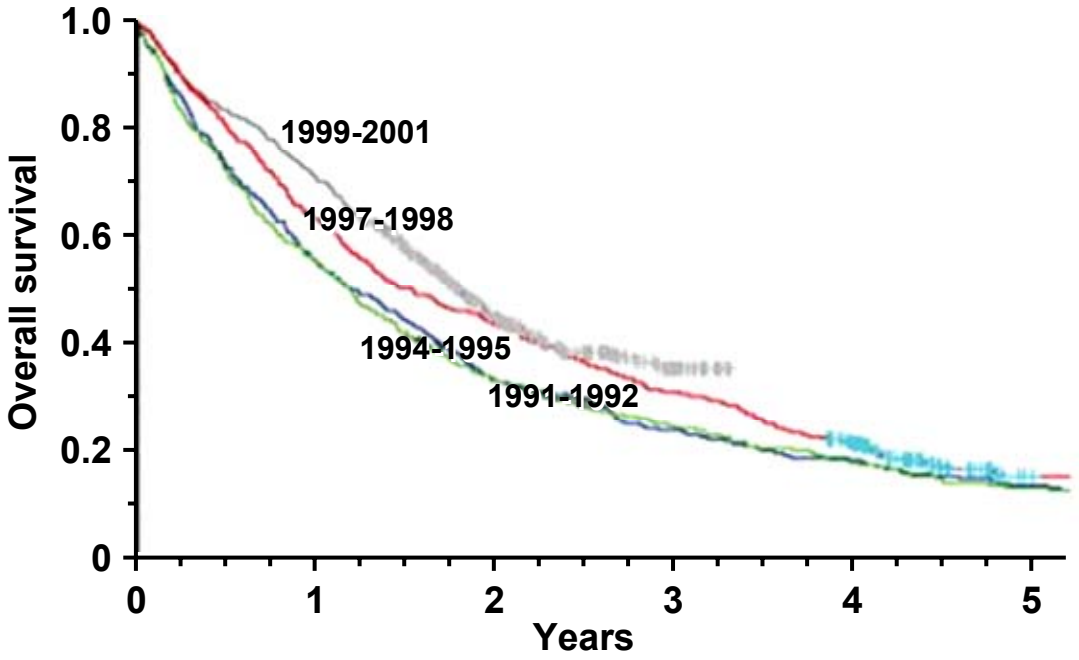
Reference	Treatment	Primary Endpoint	PFS/TTP: Medians (months) HR	Overall Survival: Medians (months) HR
Jassem et al. 2001 (n=267)	AT vs. FAC	TTP	8.3 vs. 6.2 HR not reported	23.3 vs. 18.3 HR not reported
Biganzoli et al. 2002 (n=275)	AT vs. AC	PFS	6 vs. 6 HR=1.06	20.6 vs. 20.5 HR=0.90
Sledge et al. 2003 (n=739)	AT vs. T vs. A	TTF, RR	8.2 vs. 6.0 vs. 6.3 HR not reported	19.1 vs. 22.5 vs. 22.4 HR not reported
Nabholtz et al. 2003 (n=429)	AC vs. AD	TTP	7.9 vs. 9.3 HR=1.32	21.7 vs. 22.5 HR not reported
Zielinski et al. 2005 (n=259)	FEC vs. GET	TTP	9.0 vs. 9.1 HR=0.9	24.9 vs. 29.5 HR not reported
Bontenbal et al. 2005 (n=216)	FAC vs. AD	TTP	6.6 vs. 8.0 HR not reported	16.2 vs. 22.6 HR not reported
Lueck et al. 2006 (n=340)	EP vs. XT	PFS	11.8 vs. 12.3 HR not reported	Median not reported HR not reported
Alba et al. 2010 (n=288)	Observation vs. maintenance PLD	TTP	5.1 vs. 8.4 HR=0.54	22.0 vs. 24.8 HR=0.86
Albain et al. 2008 (n=529)	T vs. GT	PFS/OS	3.9 vs. 5.9 HR=0.73	15.8 vs. 18.6 HR=0.78
Nielsen et al. 2009 (n=306)	GD vs. D	TTP	7.5 vs. 6.5 HR not reported	13.4 vs. 13.2 HR not reported

A=doxorubicin; AC=doxorubicin+cyclophosphamide; AD=doxorubicin+docetaxel; AT=doxorubicin+paclitaxel; D=docetaxel; EP=epirubicin+paclitaxel; D=docetaxel; FAC=5-fluorouracil+doxorubicin+cyclophosphamide; FEC=5-fluorouracil+epirubicin+cyclophosphamide; GD=gemcitabine+docetaxel; GET=gemcitabine+epirubicin+paclitaxel; GT=gemcitabine+paclitaxel; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; PLD=doxorubicin liposomal injection; RR=response rate; T=paclitaxel; TTF=time to treatment failure; TTP=time to disease progression; XD=capecitabine+docetaxel; XT=capecitabine+paclitaxel.

In clinical trials in the first-line MBC setting, overall survival following cytotoxic chemotherapy is approximately 20 months, with a range of 13.2 to 29.5 months. An improvement in overall survival has been historically considered the most important therapeutic objective in MBC. Over the past decade, incremental improvements in survival have been achieved in the metastatic setting, coincident with the use of effective new therapies with supportive care, and improved and more specific diagnostic techniques. The improvement in overall survival is represented in Figure 1, which illustrates the clinical impact of

these scientific advances. This improvement occurred despite the fact that few randomized trials in the first-line HER2-negative MBC setting demonstrated an effect on overall survival, as presented in Table 3.

Figure 1
Kaplan–Meier Curves for Overall Survival for Four Time Cohorts from Date of Diagnosis of Metastatic Breast Cancer



Source: 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.

It has become increasingly difficult to measure improvements in overall survival in clinical trials of MBC, particularly in patients with early metastatic disease, who may survive a relatively long time after disease progression. The use of therapies shown to be effective in subsequent lines of therapy (administration of an active agent outside of a clinical trial, crossover to an active agent within a clinical trial, or participation in another clinical trial) can affect overall survival. Evaluation of overall survival requires a large trial with extended patient follow-up, where the results may be confounded by causes of mortality unrelated to cancer. Interestingly, the trials that have shown a survival benefit were often conducted in patients with poor prognostic factors who have a short median survival and who are perhaps less likely to receive one or more subsequent treatments.

The incurability of MBC demands that new treatment strategies continue to be explored (Hamilton and Hortobagyi 2005), as this remains a disease of high unmet medical need. Additional treatment options for patients who have not received chemotherapy for their HER2-negative MBC are crucial to provide physicians and patients with flexibility in their treatment strategy and decisions. The data described in this briefing book establish Avastin, in combination with commonly used chemotherapies, as an important and effective therapeutic advance for achieving disease control in these women.

3. AVASTIN

Avastin 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) (Presta et al. 1997). This section will describe Avastin's mechanism of action and its clinical development history—both general and specific to breast cancer.

3.1 SCIENTIFIC RATIONALE AND MECHANISM OF ACTION

Angiogenesis is a physiologic process that results in the formation and growth of new blood vessels. The angiogenic process is initiated by VEGF, a diffusible cell-specific glycoprotein that plays a role in endothelial cell proliferation, survival, migration, vascular permeability, and hemodynamic responses (Ferrara and Davis-Smyth 1997). VEGF belongs to a gene family that includes five ligands (placental growth factor, VEGF-A, VEGF-B, VEGF-C, and VEGF-D) and mediates its effects by binding to two receptor tyrosine kinases (VEGFR-1 and VEGFR-2) and the neuropilin co-receptors.

Angiogenesis is a fundamental step in the transition of tumors from a dormant to a malignant state. The stage at which a tumor secretes VEGF and activates this process is referred to as the "angiogenic switch." Sustained blockade of VEGF signaling is therefore likely to delay this switch and restrain the growth of small dormant tumors, as their growth is dependent on angiogenesis (Folkman 1990a, 1990b, 1995, 1997). Increased levels of VEGF expression have been found in many human malignancies (Ferrara and Davis-Smyth 1997; von Marschall et al. 2000; Luo et al. 2001) and are often correlated with poor survival (Gasparini et al. 1997, Foekens 2001). In breast cancer, VEGF levels are increased in all major histologic subtypes, and an increased density of microvessels in these tumors correlates with disease recurrence and reduced survival (Weidner et al. 1991, 1992).

Inhibition of angiogenesis with targeted agents, both alone and in combination with other cytotoxic or targeted therapies, has been shown to be an effective approach to delaying the growth of multiple tumor types, including breast cancer. Avastin is a humanized monoclonal antibody that selectively neutralizes the biologic activity of VEGF, resulting in anti-vascular and anti-angiogenic mechanisms of action. Avastin's mechanism of action is not dependent on

currently known molecular signatures of breast cancer, making it broadly applicable across all patient subsets. Furthermore, Avastin has been shown, in both animals and patients, to combine well with diverse types of cytotoxic chemotherapy, further supporting its broad clinical utility.

By acting directly on tumor vasculature, Avastin provides a complementary strategy when combined with chemotherapy and other agents that directly target the tumor cell. By depleting VEGF, an endothelial cell survival factor, Avastin can sensitize the tumor vasculature to chemotherapy-induced damage, thereby enhancing the activity of both agents. These anti-vascular effects may result in tumor shrinkage, which is reflected clinically in the objective response rate. The anti-angiogenic activity of Avastin may then maintain these tumors in a dormant state by preventing recruitment of new tumor vasculature. Furthermore, Avastin "normalizes" the tumor vasculature, resulting in more stable, less permeable vessels, which has the potential to limit hematogenous spread of malignant cells.

In summary, the anti-angiogenic, anti-vascular, and potential anti-metastatic activities of Avastin, as a single agent and in combination with multiple cytotoxic agents, are relevant to its use in breast cancer.

3.2 AVASTIN CLINICAL DEVELOPMENT PROGRAM AND U.S. REGULATORY HISTORY

On the basis of Avastin's mechanism of action and nonclinical evidence, a comprehensive clinical development plan was initiated for Avastin in a wide variety of malignant conditions, spanning 30 different tumor types in adjuvant and metastatic settings. Avastin has received market approval for the treatment of patients with metastatic colorectal cancer, advanced non-squamous, non–small cell lung cancer, and metastatic renal cell carcinoma, and accelerated approval for metastatic HER2-negative breast cancer and relapsed glioblastoma (see the Avastin® U.S. Package Insert; provided in Appendix B).

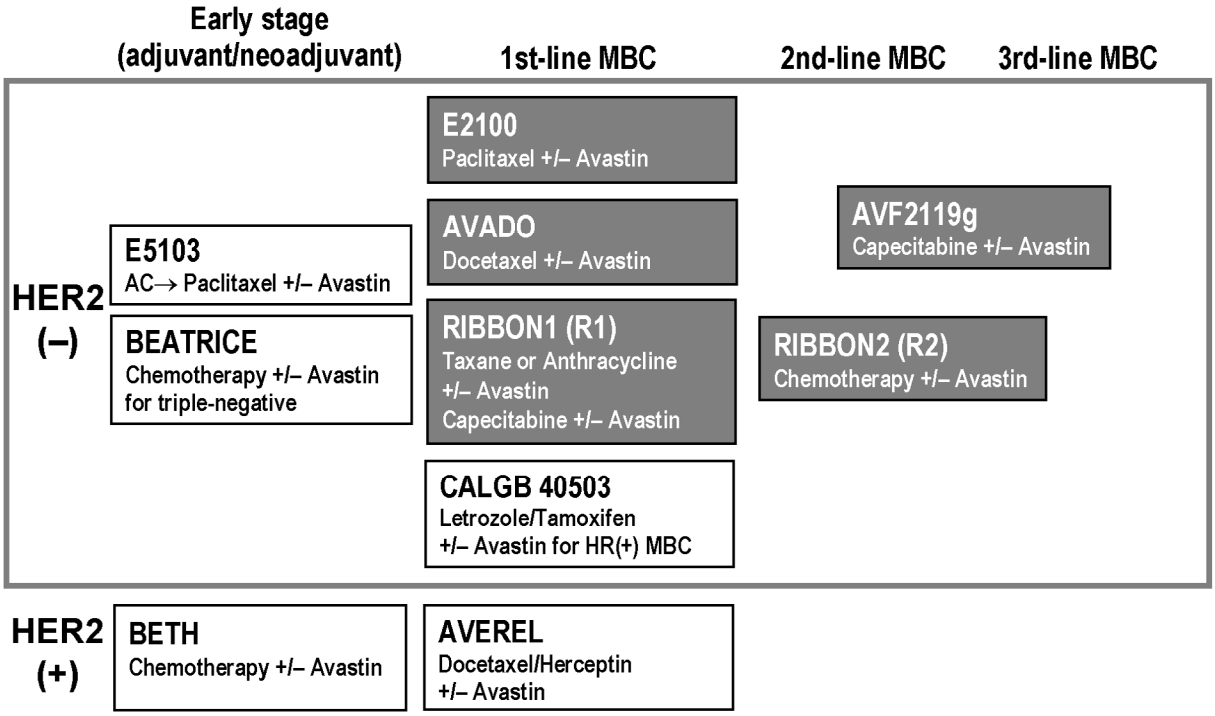
The overall safety profile of Avastin, as reflected in the Avastin® U.S. Package Insert, is based on clinical trial data and postmarketing experience. Data have been analyzed for more than 13,300 patients who have received Avastin either as a single agent or in combination with chemotherapy or other therapies in completed clinical trials. As of February 2010, more than 812,000 patients have

been exposed to Avastin as a marketed product or in a clinical trial (Genentech data on file).

3.3 AVASTIN CLINICAL DEVELOPMENT PROGRAM IN BREAST CANCER

Genentech is committed to a comprehensive development program in breast cancer, as evidenced by the multiple randomized, Phase III trials of Avastin in combination with chemotherapy, hormonal therapy, or trastuzumab for the treatment of patients with early-stage breast cancer or MBC that are completed or are ongoing. Figure 2 presents an overview of the Phase III clinical development program to potentially support expanded labeling for Avastin in breast cancer (refer to Appendix C for details of each study).

Figure 2
Avastin Phase III Clinical Development Program



AC = doxorubicin + cyclophosphamide; HR = hormone receptor; MBC = metastatic breast cancer.
Note: AVF2119g also enrolled a small subgroup of HER2-positive patients and/or first-line patients.

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 Avastin (Cobleigh et al. 2003).

On the basis of the safety and activity observed with single-agent Avastin at a dose of 10 mg/kg every other week, two Phase III trials were initiated in distinctively different patient populations to further investigate Avastin in combination with chemotherapy in MBC: AVF2119g (in previously treated MBC, i.e., the second- and third-line MBC setting) and E2100 (in the first-line MBC setting).

AVF2119g was a multicenter, randomized, open-label, controlled trial that investigated the combination of capecitabine + Avastin compared with capecitabine alone (Miller et al. 2005; see Appendix C for further details on the study design). This study was conducted in the United States and enrolled a heterogeneous patient population with advanced MBC; approximately 23% of patients had HER2-positive tumors. Eligible patients had MBC that had progressed following one or two regimens for metastatic disease, or following adjuvant therapy containing both an anthracycline and a taxane, with disease recurrence within 12 months. The study did not meet its primary objective of PFS; however, an increase in objective response rate suggested Avastin activity in MBC. The safety profile observed in AVF2119g was similar to that observed in other MBC studies and across other indications. Data from AVF2119g have been previously reviewed by the FDA, and safety data are included in the Avastin® U.S. Package Insert.

E2100 was a multicenter, randomized, open-label, controlled trial that investigated the combination of paclitaxel + Avastin compared with paclitaxel alone in patients who had not received chemotherapy for their HER2-negative MBC (see Appendix C for further details on the study design). The combination of Avastin with first-line paclitaxel resulted in a statistically significant and clinically meaningful improvement in PFS based on an independent review of radiographs and clinical information ($HR = 0.48$; $p < 0.0001$), with a 5.5-month increase in median PFS (from 5.8 to 11.3 months) that was consistent across patient subgroups and robust according to multiple sensitivity analyses. The safety profile for Avastin in E2100 was consistent with the profile established in previous trials in MBC and other indications.

On the basis of the efficacy and safety data from E2100, Genentech and F. Hoffmann–La Roche initiated a broad clinical development plan in advanced and early breast cancer (see Figure 2), in combination with commonly used

chemotherapies reflective of clinical practice and in a spectrum of breast cancer patient populations (e.g., HER2-positive, triple-negative, and hormone-sensitive disease).

To complement the data from E2100, two additional studies (AVADO and RIBBON1) were designed to investigate the effect of combining Avastin with commonly used chemotherapeutic agents for the first-line treatment of patients with HER2-negative MBC (see Appendix C for further details on the study design):

- Taxanes: docetaxel (AVADO and RIBBON1) or nab-paclitaxel (RIBBON1)
- Anthracycline-based regimens (RIBBON1)
- Capecitabine (RIBBON1)

PFS, defined as the time from study entry until disease progression or death, was chosen as the primary endpoint for these two randomized, controlled, Phase III trials because it is a direct measure of treatment effect. Specifically,

- PFS is an accepted, clinically meaningful, and objective measure of benefit for patients with MBC. Prolonging the time to disease progression is clinically meaningful for patients, as it delays the onset of disease-related symptoms and the side effects from a new therapy, avoids the psychological consequences associated with disease progression and changing therapy, and eliminates the uncertainty as to whether new treatment will be effective.
- PFS has the following advantages compared with overall survival: minimization of the potential impact of subsequent therapy or crossover, measurement of cytostatic activity, inclusion of survival data in the assessment, limited confounding by causes of post-progression death not related to cancer, as well as requirement of smaller sample sizes and shorter follow-up.
- Potential investigator bias in the assessment of PFS can be minimized by implementing a placebo control (included in AVADO and RIBBON1) and/or employing an independent review of tumor assessments (included in E2100 and RIBBON1).
- The extent of disease in MBC can be reliably measured on radiographs; therefore, PFS is appropriate in this setting (Therasse et al. 2000).

Table 4 provides an overview of the three studies of Avastin as first-line treatment for MBC.

Table 4
Overview of Phase III Trials of Avastin as First-Line Treatment for Metastatic Breast Cancer: E2100, AVADO, and RIBBON1

Study	Design	Treatment	Patients Enrolled	Geographic Region	Primary Endpoint
E2100	Phase III, multicenter, randomized, open-label, controlled trial 1:1 randomization	Paclitaxel alone or Paclitaxel + Avastin	722	Primarily United States (plus Canada, South Africa, and Peru)	PFS
AVADO	Phase III, multicenter, randomized, double-blind, placebo-controlled, three-arm trial 1:1:1 randomization	Docetaxel + placebo or Docetaxel + Avastin 7.5 mg/kg or Docetaxel + Avastin 15 mg/kg	736	Western Europe, Eastern Europe, Australia, Canada, East Asia, Central and South America	PFS
RIBBON1	Phase III, multicenter, randomized, double-blind, placebo-controlled trial 2:1 randomization	1) Taxane (docetaxel or nab-paclitaxel) + Avastin/placebo or Anthracycline-based chemotherapy + Avastin/placebo or 2) Capecitabine + Avastin/placebo	1) Taxane group: 307 Anthracycline group: 315 2) Capecitabine group: 615	United States, Western Europe, Eastern Europe, Australia, Canada, East Asia, Central and South America	PFS

PFS = progression-free survival.

While differing in chemotherapy regimens and design, these trials shared the same objective of demonstrating improved clinical benefit, as measured by PFS and objective response rate, when Avastin was combined with commonly used chemotherapy regimens for the first-line treatment of patients with HER2-negative MBC.

RIBBON1 consisted of two independently powered comparisons under a single protocol: the taxane/anthracycline comparison and the capecitabine comparison. Sample sizes were determined for each comparison independently, and the two comparisons were also analyzed separately.

Genentech shared the RIBBON1 protocol with the FDA prior to enrollment of the first patient and had a discussion regarding the study design as part of a general Avastin development plan discussion at a Type B meeting on 10 January 2006. Genentech also discussed the Statistical Analysis Plan (SAP) for both AVADO

and RIBBON1 with the FDA prior to conducting the efficacy analysis. Genentech incorporated key FDA feedback into the Avastin MBC clinical development program, specifically,

- In response to FDA feedback received via correspondence, Genentech increased the sample size of the capecitabine comparison in RIBBON1 to fully power this cohort (Protocol Amendment 3; dated 20 February 2007) in order to ascertain the clinical benefit of Avastin in combination with capecitabine. Genentech also revised the RIBBON1 SAP to address the FDA's recommendation to include secondary analyses evaluating PFS within each chemotherapy class.
- Although RIBBON1 is a placebo-controlled and double-blind study, an independent review of progression endpoints was conducted in order to ensure that bias was minimized. During a Type C meeting held on 18 September 2007 to discuss the RIBBON1 SAP, the FDA agreed with the Genentech proposal to conduct the independent review and use the results of the independent review as a secondary analysis to support the primary endpoint of investigator-assessed PFS.

Genentech also received the following feedback from the FDA, which was not incorporated into the Avastin MBC clinical development program:

- In RIBBON1, Genentech did not increase the sample size of the taxane/anthracycline comparison to fully power each comparison. The design of RIBBON1 was intended to reflect clinical practice and was based on the rationale that inhibition of VEGF activity is not directly dependent on the combination chemotherapy and that Avastin has been successfully used with a variety of agents (e.g., platinums, taxanes, topoisomerase inhibitors, and anti-metabolites) across multiple indications. However, to ensure balance within the chemotherapy subgroups, chemotherapy class was added as a stratification factor to the protocol.
- An independent review of progression endpoints was not implemented for AVADO because this trial was designed as a double-blind, placebo-controlled study and two other Phase III trials (E2100 and RIBBON1) included an independent review to confirm the robustness of investigator assessments. In addition, previous independent reviews for studies in breast cancer and other indications have been consistent with investigator assessments; therefore, Genentech believed that bias was already minimized with a placebo-controlled study design.

Appendix D summarizes the key regulatory interactions between Genentech and the FDA and the key events pertinent to decisions regarding the clinical development of Avastin as first-line treatment for MBC in AVADO and RIBBON1.

3.4 ACCELERATED APPROVAL FOR AVASTIN IN METASTATIC BREAST CANCER

On 22 February 2008, Genentech was granted marketing approval for Avastin for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer under the accelerated approval of biologic product regulations (21 CFR §601.40–46) on the basis of data from E2100. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as the basis for approvals of products intended for serious or life-threatening illnesses or conditions. Approval under these regulations requires that the Sponsor conducts adequate and well-controlled studies to further define the degree of clinical benefit to patients and to conduct such studies with due diligence.

For this accelerated approval, there was one postmarketing commitment subject to the reporting requirements of 21 CFR §601.70:

- To submit an efficacy supplement containing the final study reports (including summary analyses and primary datasets) and revised labeling based on the results from both the following studies:

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

  RIBBON1, “A Multicenter, Phase III, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer”

Further to the requirements outlined in the approval letter, the FDA confirmed in the minutes for the Type B meeting on 26 February 2009 that the basis for conversion to full approval is “demonstrated improvement in PFS and evidence that survival is not impaired.”

AVADO and RIBBON1 were underway when the accelerated approval for Avastin in MBC was granted. Genentech has proceeded with due diligence, and AVADO and RIBBON1 were completed in a timely manner. The FDA provided additional feedback to Genentech in formal meetings upon data availability:

- During a Type C meeting held on 7 October 2008, the FDA requested that the data from AVADO and RIBBON1 be submitted in two separate sBLAs. As such, Genentech has provided the data from each study in separate sBLAs.
- During a Type B pre-sBLA meeting held on 26 February 2009 to discuss the proposed contents of the supplements for AVADO and RIBBON1, the FDA highly recommended that Genentech provide updated overall survival data for each study in the submission of the respective sBLA. In response, Genentech included updated overall survival data for each study in the original submission.

On 16 November 2009, Genentech submitted two sBLAs to address the postmarketing commitment as described above. These data demonstrated that the two additional randomized, controlled, Phase III clinical trials (AVADO and RIBBON1) have verified and further defined the clinical benefit observed in E2100, with the consistent and reliable demonstration of an improvement in PFS. The totality of the data also demonstrates that the safety profile of Avastin in combination with commonly used chemotherapies in MBC was well established and consistent with that observed in other indications and described in the Avastin® U.S. Package Insert.

Therefore, on the basis of data from AVADO and RIBBON1, Genentech is requesting

- Conversion of the accelerated approval based on E2100 to full approval on the basis of criteria agreed upon with the FDA for the following indication statement:

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

- Expansion of the Avastin label to include the following indication statement:

  > Avastin, in combination with taxane-based, anthracycline-based, or capecitabine chemotherapy, is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

4. EFFICACY AND SAFETY OF AVASTIN IN FIRST-LINE METASTATIC BREAST CANCER STUDIES

This section summarizes the data to address the criteria for the postmarketing commitment to convert the accelerated approval, as agreed upon with the FDA, and provides substantial evidence of clinical benefit for Avastin in combination with several types of chemotherapy for the first-line treatment of patients with HER2-negative MBC.

In all three trials (E2100, AVADO, and RIBBON1), the study population consisted of patients with locally recurrent or metastatic HER2-negative adenocarcinoma of the breast. Treatment with Avastin was planned to continue until disease progression, treatment-limiting toxicity, or death due to any cause. However, there were some differences in study design, including the following:

- **Background chemotherapy:** Weekly paclitaxel was used in E2100, and docetaxel (every 3 weeks) was used in AVADO. RIBBON1 allowed investigators to choose among chemotherapies including docetaxel, nab-paclitaxel, anthracycline-based chemotherapy, and capecitabine.
- **Dose of Avastin:** AVADO included two treatment arms that combined docetaxel with Avastin at either 7.5 mg/kg or 15 mg/kg every 3 weeks. Because E2100 and RIBBON1 evaluated only the Avastin dose equivalent to 15 mg/kg every 3 weeks, efficacy conclusions from AVADO are based only on patients treated at that dose; efficacy results for the 248 patients randomized to 7.5 mg/kg are provided in Appendix E.
- **Open-label Avastin use:** In E2100, patients in the paclitaxel + Avastin arm who discontinued paclitaxel prior to disease progression were allowed to continue single-agent Avastin until disease progression. However, patients in the paclitaxel-alone arm who developed disease progression were not allowed to cross over to receive Avastin. In AVADO and RIBBON1, patients in either treatment arm could receive open-label Avastin after disease progression and at the time of study unblinding. Patients who crossed over to open-label Avastin after disease progression (but prior to study unblinding) were not told their blinded treatment assignment.
- **Chemotherapy duration:** In RIBBON1, non-anthracycline chemotherapy was allowed to continue until disease progression. Anthracyclines were discontinued after eight cycles, whereas other agents in the regimen (e.g., cyclophosphamide) were continued. In E2100, patients were treated with paclitaxel until disease progression, whereas in AVADO, patients received docetaxel for a maximum of nine cycles (27 weeks).

- **Adverse event collection:** In E2100, Grade 3–5 non-hematologic and Grade 4 and 5 hematologic adverse events were collected. In AVADO, all adverse events of any grade were collected. In RIBBON1, selected adverse events associated with Avastin, adverse events leading to treatment discontinuation, and all serious adverse events were collected.

These and other differences in study design are outlined in Table 5.

Schemas illustrating the design of each study are provided in Appendix C.

Table 5

Comparison of E2100, AVADO, and RIBBON1

	E2100 (Open Label)	AVADO (Double Blind)	RIBBON1 (Double Blind)
Chemotherapy	Paclitaxel 90 mg/m^2 IV qwk for 3 weeks followed by 1 week of rest, until PD, death, unacceptable toxicity, or patient withdrawal. Each cycle was 4 weeks.	Docetaxel 100 mg/m^2 IV q3wk for a maximum of 9 cycles or until PD, death, unacceptable toxicity, or patient withdrawal. Each cycle was 3 weeks.	Investigator's choice of chemotherapy (declared prior to randomization). Chemotherapy given until PD, death, unacceptable toxicity, or patient withdrawal. Each cycle was 3 weeks. Taxane: • Docetaxel 75–100 mg/m^2 IV q3wk • Nab-paclitaxel 260 mg/m^2 IV q3wk Anthracycline-based • FEC/FAC/AC/EC q3wk, with minimum 6 cycles and maximum 8 cycles of anthracycline (if maximum cumulative dose of anthracycline was reached, other components of chemotherapy could continue) Capecitabine: 1000 mg/m^2 oral twice daily on Days 1–14 of every 3-week cycle
AE collection	Grade 3–5 non-hematologic and Grade 4 and 5 hematologic AEs	All AEs	Selected AEs; serious AEs, and AEs resulting in discontinuation of study drug.
Sample size (intent-to-treat)	Total n = 722 Pac alone: n = 354 Pac + Avastin: n = 368	Total n = 736 Doc + Placebo: n = 241 Doc + Avastin7.5: n = 248 Doc + Avastin15: n = 247	Total n = 1237 T/Anth: n = 622 T/Anth + Placebo: n = 207 (T: n = 104, Anth: n = 103) T/Anth + Avastin: n = 415 (T: n = 203, Anth: n = 212) Cap: n = 615 Cap + Placebo: n = 206 Cap + Avastin: n = 409

AC = doxorubicin and cyclophosphamide; AEs = adverse events; Cap = capecitabine; Doc = docetaxel; EC = epirubicin and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; FPI = first patient in; LPI = last patient in; Pac = paclitaxel; PD = progressive disease; T/Anth = taxane/anthracycline.

Table 5 (cont'd)
Comparison of E2100, AVADO, and RIBBON1

	E2100 (Open Label)	AVADO (Double Blind)	RIBBON1 (Double Blind)
Enrollment period	FPI: 21 December 2001 LPI: 26 May 2004 ~29 months	FPI: 20 March 2006 LPI: 12 April 2007 ~13 months	FPI: 15 December 2005 LPI: August 2007 ~21 months
Follow-up at data cutoff	PFS data cutoff: 9 February 2005 (~3 years, 1 month from FPI; ~8.1 months from LPI). Extended survival data cutoff at 481 deaths: 21 October 2006.	PFS data cutoff: 31 October 2007 (~19.5 months from FPI; 6.5 months from LPI). Extended survival data cutoff: 30 April 2009 (25 months after LPI).	PFS data cutoff: 31 July 2008 (~31.5 months from FPI; 11.5 months from LPI). Extended survival data cutoff: 23 February 2009 (18 months after LPI).
Tumor assessment schedule	Every 12 weeks while on protocol therapy until PD. For patients who had discontinued protocol therapy, every 3 months for up to 2 years from randomization and every 6 months from 2 to 5 years from randomization, until PD. Tumor response and disease progression were evaluated using RECIST.	Every 9 weeks until Week 36; every 12 weeks thereafter until PD. For patients who discontinued protocol therapy, every 3 months after discontinuation of therapy until PD. Tumor response and disease progression were evaluated using RECIST.	Every 9 weeks until PD, regardless whether patients had discontinued from study treatment. Tumor response and disease progression were evaluated using RECIST.
Post-PD Avastin use	Not available.	Patients in either treatment arm could receive Avastin post-PD post-study phase.	Patients in either treatment arm could receive Avastin post-PD post-study phase.
Sponsorship	Independently conducted by the Eastern Cooperative Oncology Group as an Intergroup study and sponsored by the National Cancer Institute Cancer Therapy Evaluation Program (NCI-CTEP).	Conducted and Sponsored by Roche.	Conducted and Sponsored by Genentech.

AC = doxorubicin and cyclophosphamide; AEs = adverse events; Cap = capecitabine; Doc = docetaxel; EC = epirubicin and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; FPI = first patient in; LPI = last patient in; Pac = paclitaxel; PD = progressive disease; T/Anth = taxane/anthracycline.

All three trials (E2100, AVADO, and RIBBON1) were conducted according to Good Clinical Practice (GCP), International Conference for Harmonization (ICH) Guidelines, and in accordance with local and regional health authority regulations.

Compliance with the protocols' procedures will high, with fewer than 7% of patients having a violation for eligibility criteria. An average of 97% of all radiologic scans across study visits were assessed as planned.

A total of 2695 patients were enrolled in E2100, AVADO, and RIBBON1. Key patient demographics were similar across the three studies and balanced across treatment arms (see Table 6). The median age of enrolled patients ranged between 55 and 57 years; the majority of patients were of the White race and were post-menopausal.

Table 6
Baseline Demographics of Patients in E2100, AVADO, and RIBBON1

	E2100		AVADO		RIBBON1 T/Anth Comparison		RIBBON1 Cap Comparison	
	Pac (n=354)	Pac+ Avastin (n=368)	Doc+ Placebo (n=241)	Doc+ Avastin (n=247)	T/Anth+ Placebo (n=207)	T/Anth+ Avastin (n=415)	Cap+ Placebo (n=206)	Cap+ Avastin (n=409)
Age (yr)								
Mean	55.4	55.5	53.5	53.6	54.3	55.7	57.1	56.6
Median	55	56	55	55	55	55	57	56
≥50	68.6%	65.8%	64.3%	62.3%	63.3%	71.1%	73.8%	70.9%
Race								
White	75.1%	77.2%	82.6%	84.2%	84.5%	82.2%	76.2%	75.3%
Menopausal status								
n	259	258	194	213	193	368	185	365
Pre-menopausal	21.2%	24.4%	27.8%	28.6%	39.4%	34.5%	32.4%	32.9%

Cap=capecitabine; Doc=docetaxel; Pac=paclitaxel; T/Anth=taxane/anthracycline.

Known prognostic factors for patients with untreated, locally recurrent or metastatic breast cancer were balanced across treatment arms within each study (see Table 7). Patients in the three studies displayed unfavorable disease characteristics typical of a population requiring treatment with chemotherapy, as evidenced by the proportion of patients with a disease-free interval of ≤24 months (30% to 45%), with at least three metastatic sites (29% to 50%), and with visceral disease (64% to 77%). Additionally, 45% to 76% of patients had received prior adjuvant treatment. Compared with AVADO and RIBBON1, E2100 enrolled a higher percentage of patients with the following prognostic factors: hormone receptor–negative disease, triple-negative disease, non-measurable disease at baseline, and fewer than three metastatic sites at baseline. The distribution of these baseline factors was similar across AVADO and RIBBON1.

Table 7

Baseline Disease Characteristics of Patients in E2100, AVADO, and RIBBON1

	E2100		AVADO		RIBBON1 T/Anth Comparison		RIBBON1 Cap Comparison	
	Pac (n=354)	Pac+ Avastin (n=368)	Doc+ Placebo (n=241)	Doc+ Avastin (n=247)	T/Anth+ Placebo (n=207)	T/Anth+ Avastin (n=415)	Cap+ Placebo (n=206)	Cap+ Avastin (n=409)
Hormone receptor status [a]								
n	347	359	241	246	199	402	198	403
Positive (ER+ and/or PgR+)	65.4%	64.6%	78.4%	76%	76.9%	76.1%	73.7%	77.4%
Negative (ER− and PgR−)	34.6%	35.4%	21.6%	24%	23.1%	23.9%	26.3%	22.6%
Triple-negative [b]								
Yes	31.1%	33.2%	21.6%	23.5%	22.2%	23.1%	24.3%	21.3%
No	64.7%	63.9%	78.4%	76.1%	73.9%	73.7%	71.8%	76.8%
Unknown	4.2%	3.0%	0.0%	0.4%	3.9%	3.1%	3.9%	2.0%
Prior adjuvant therapy								
n	354	368	241	247	207	415	206	409
Yes	65.3%	66.3%	64.7%	67.6%	46.9%	44.8%	75.7%	70.4%
Visceral disease								
n	354	368	241	247	207	415	206	407
Yes	68.9%	64.1%	73.0%	76.9%	73.4%	68.9%	71.4%	67.5%
Number of metastatic sites								
≥3	28.8%	28.8%	41.3%	50.0%	44.9%	45.3%	45.1%	43.3%
Disease-free interval (months)								
n	354	368	241	247	206	414	206	407
≤24	41.2%	40.8%	36.5%	29.6%	44.7%	41.1%	31.1%	34.6%

Cap=capecitabine; Doc=docetaxel; ER=estrogen receptor; Pac=paclitaxel; PgR=progesterone receptor; T/Anth=taxane/anthracycline.

[a] Hormone receptor status was unknown if either ER or PgR status was negative and the other was unknown, or if the status of both receptors was unknown.

[b] Patients were considered to have triple-negative disease if their tumor was negative for three receptors (HER2, ER, and PgR).

As stated above, a total of 2695 patients were enrolled in E2100, AVADO, and RIBBON1. For the purposes of safety evaluations in these three studies, all 2661 patients treated with study drug were included in analyses (safety population).

Two dose regimens of Avastin were evaluated in AVADO: 15 mg/kg every 3 weeks and 7.5 mg/kg every 3 weeks. The differences in PFS and objective response rate between the low-dose arm and the control arm were statistically significant; however, the results for the high-dose arm were numerically superior. No difference in overall survival was seen between the low-dose arm and the control arm. On the basis of these results and to allow a clear comparison with E2100 and RIBBON1, the low-dose arm of AVADO (n=248) was not included in the efficacy analyses; data from 2447 patients were included in these analyses. Efficacy results for patients who received the low dose of Avastin in AVADO are provided in Appendix E.

4.1 PROGRESSION-FREE SURVIVAL

As described in Section 3.3, PFS was the primary endpoint for all three studies, and was prospectively defined as the time from randomization until disease progression or death. In the event that a patient received non-protocol anti-cancer therapy (NPT) prior to progression, PFS was censored at the last tumor assessment prior to the start of NPT.

The clinical trial designs and analysis plans were developed to ensure that measurements of PFS were reliable and robust. All three studies employed blinding to minimize bias in estimates of the treatment effect. AVADO and RIBBON1 were double-blind, placebo-controlled trials, and Study E2100 incorporated a retrospective, blinded independent review of radiologic and clinical data. In all studies, fewer than 7% of patients violated eligibility criteria, and an average of 97% of all radiologic scans across study visits were assessed as planned (compliance over the first year was 94% for E2100, 97% for AVADO, and 97% for both comparisons of RIBBON1). The combined data from these three studies included over 1500 progression events or deaths, a sample size that provides precision to the PFS results and the evaluation of Avastin's clinical benefit.

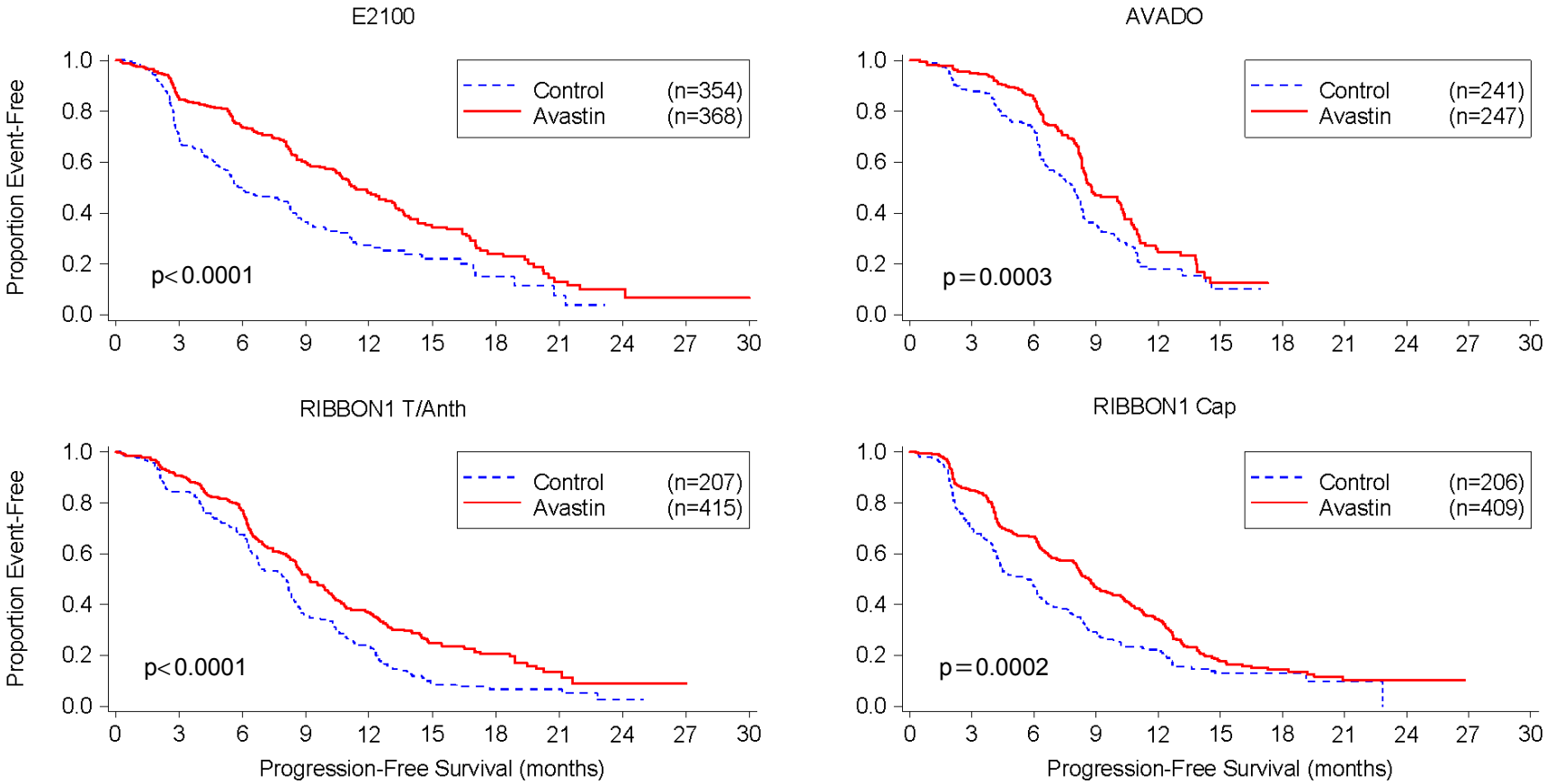
A statistically significant improvement in PFS in favor of the Avastin-containing arm was demonstrated in all four efficacy comparisons. Figure 3 shows the Kaplan–Meier curves; at all times, there was a clear separation of the curves favoring the Avastin-containing arm. The hazard ratios ranged from 0.48 to 0.69, corresponding to a 31% to 52% reduction in the risk of disease progression or death prior to disease progression (Figure 4). In all four comparisons,

the observed hazard ratios exceeded the hazard ratios of 0.7–0.75 that were targeted in the study protocols.

The variability in the estimates of treatment benefit across these four comparisons is consistent with chance variation, as indicated by the broadly overlapping confidence intervals and a treatment-by-study interaction p-value of >0.2. Nevertheless, there is the possibility of some differences in magnitude of effect across these studies.

Figure 3

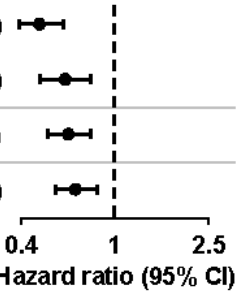
Kaplan–Meier Curves for Progression-Free Survival: E2100, AVADO, and RIBBON1



RIBBON1 Cap = capecitabine comparison of RIBBON1; RIBBON1 T/Anth = taxane/anthracycline comparison of RIBBON1.

Figure 4
Progression-Free Survival in E2100, AVADO, and RIBBON1

Study		Non-AVF arm N	Non-AVF arm Event	Non-AVF arm Median, mo	AVF arm N	AVF arm Event	AVF arm Median, mo	Hazard ratio (95% CI)
E2100	Pac+AVF vs Pac	354	184	5.8	368	173	11.3	0.48 (0.39, 0.61)
AVADO	Doc+AVF vs Doc+PL	241	152	7.9	247	134	8.8	0.62 (0.48, 0.79)
R1-T/Anth	T/Anth+AVF vs T/Anth+PL	207	160	8.0	415	249	9.2	0.64 (0.52, 0.80)
R1-Cap	Cap+AVF vs Cap+PL	206	162	5.7	409	291	8.6	0.69 (0.56, 0.84)



AVF = Avastin; Cap = capecitabine; CI = confidence interval; Doc = docetaxel; Pac = paclitaxel; PL = placebo; R1-Cap = RIBBON1, capecitabine comparison; R1-T/Anth = RIBBON1, taxane/anthracycline comparison; T/Anth = taxane/anthracycline.

Note: E2100 stratification factors: disease-free interval, prior adjuvant therapy, number of metastatic sites, and estrogen receptor status; AVADO stratification factors: region, prior adjuvant therapy, measurable disease, and hormone receptor status; RIBBON1 stratification factors: disease-free interval, prior adjuvant therapy, number of metastatic sites, and choice of chemotherapy (T/Anth comparison only).

For all three studies, the hazard ratio was prospectively chosen as the basis of the primary analysis. The hazard ratio is generally preferred by clinical researchers because it is a global assessment of the magnitude of treatment benefit that uses all the data. A drawback of the hazard ratio is that it is difficult to express on a time scale that may be more intuitive to physicians and patients.

One approach to describe magnitude of benefit on a time scale is to calculate the difference in median PFS for the two treatment arms (Figure 4 and Table 8). The difference in median PFS across the four comparisons ranged from 0.9 months in AVADO to 5.5 months in E2100. A drawback of this approach is that it uses only a single arbitrary point on the curve, which is subject to greater variability, and patient outcomes after the median are not taken into consideration.

An alternative method of describing benefit on a time scale is to calculate the difference in average PFS for the two treatment arms (Karrison 1997). This corresponds to the average difference between the two Kaplan–Meier curves. Like the hazard ratio, this method uses all of the available information, but it has the advantage of being measured in time units. The differences in average PFS across the four efficacy comparisons ranged from 1.5 months in AVADO to 4.1 months in E2100 (Table 8), demonstrating less variability than the difference in medians.

Table 8
Magnitude of Progression-Free Survival Benefit across Studies

Study	Hazard Ratio (95% CI)	Difference in Median PFS (Months)	Difference in Average PFS (95% CI) [a]
E2100	0.48 (0.39, 0.61)	5.5	4.1 (2.5, 5.8)
AVADO	0.62 (0.48, 0.79)	0.9	1.5 (0.6, 2.4)
R1-T/Anth	0.64 (0.52, 0.80)	1.2	2.6 (1.4, 3.9)
R1-Cap	0.69 (0.56, 0.84)	2.9	2.5 (1.3, 3.8)

CI = confidence interval; PFS = progression-free survival; R1-Cap = RIBBON1, capecitabine comparison; R1-T/Anth = RIBBON1, taxane/anthracycline comparison.

[a] Average PFS in months calculated from Kaplan–Meier estimates. The standard error of the difference in average PFS was estimated using Greenwood's formula.

Regardless of which measure of treatment benefit is used—hazard ratios, medians, or average PFS—an observed treatment benefit was consistently observed in favor of patients in the Avastin-containing arms.

Several exploratory and sensitivity analyses were performed on the PFS data from all three trials (refer to Appendix F for a description of the methodology). With the use of PFS as a primary endpoint, a common concern is the minimization of bias, which was addressed in the study designs with inclusion of placebo controls and independent radiology review. Results from this independent review in RIBBON1, a secondary analysis, were consistent with those of the primary analysis: HR = 0.77 (95% CI: 0.60, 0.99; log-rank p = 0.040) for the taxane/anthracycline comparison and HR = 0.68 (95% CI: 0.54, 0.86; log-rank p = 0.0011) for the capecitabine comparison.

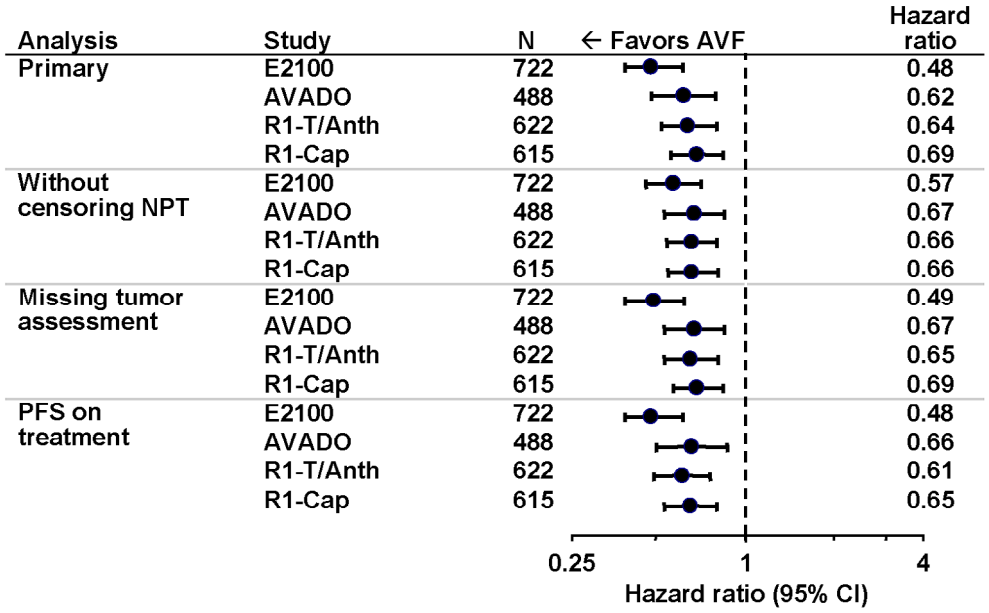
Because PFS results may also be affected by differences in PFS definitions and tumor assessments, multiple sensitivity analyses have been performed to demonstrate the robustness and reliability of the primary results, including the following:

- **Without censoring for non-protocol anti-cancer therapy.** This analysis differed from the primary PFS analysis, in which patients were censored at the start of NPT. For patients who started NPT prior to progressive disease, any progression or death occurring after initiation of NPT was considered a PFS event. Otherwise, PFS was censored at the last tumor assessments.
- **Missing tumor assessments.** This analysis assessed the impact of missing scans on the PFS results. For patients with a PFS event who missed scheduled assessments or had assessments that were deemed "unable to assess" immediately prior to progressive disease, the date of progression was replaced with the date of the first missing assessment.

- **PFS on treatment.** This analysis assessed the impact of late deaths after treatment discontinuation on the PFS analysis. For patients in AVADO and RIBBON1 who died or had disease progression >63 days after the last dose of blinded study drug, PFS was censored at the last tumor assessment within 63 days (one tumor assessment cycle) after the last dose of blinded study drug. For E2100, an 84-day cutoff was used.

As shown in Figure 5, the hazard ratio results of all sensitivity analyses indicated an improvement in PFS that was similar to the primary analysis results in each study, confirming a robust and consistent treatment effect. Specifically, the conclusion of benefit in each of these studies does not depend on the statistical or analytical approach used.

Figure 5
Sensitivity Analyses of Progression-Free Survival



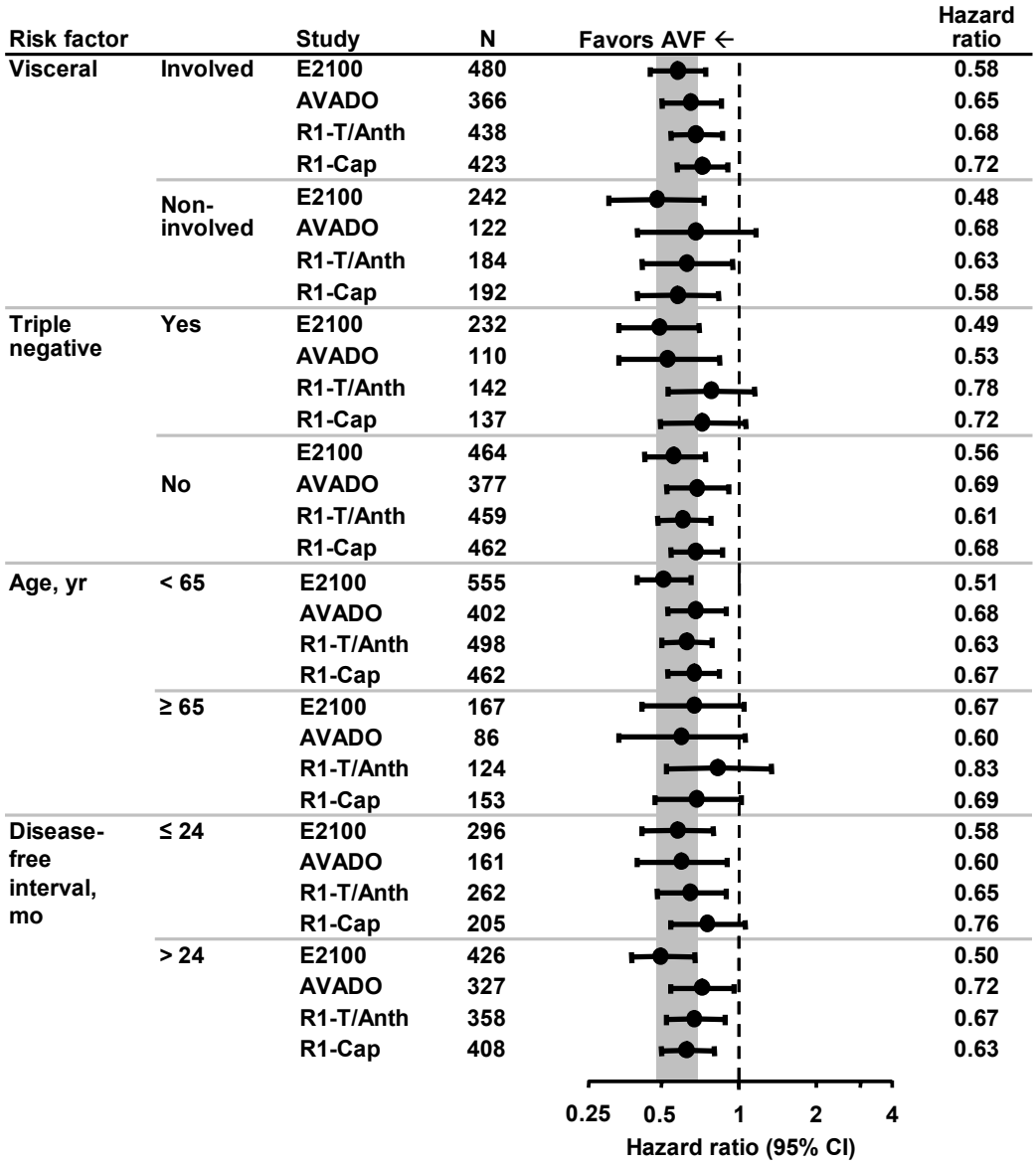
AVF = Avastin; CI = confidence interval; NPT = non-protocol anti-cancer therapy; PFS = progression-free survival; R1-Cap = RIBBON1, capecitabine comparison; R1-T/Anth = RIBBON1, taxane/anthracycline comparison.

Note: E2100 stratification factors: disease-free interval, prior adjuvant therapy, number of metastatic sites, and estrogen receptor status; AVADO stratification factors: region, prior adjuvant therapy, measurable disease, and hormone receptor status). RIBBON1 stratification factors: disease-free interval, prior adjuvant therapy, number of metastatic sites, and choice of chemotherapy (T/Anth comparison only).

Additional sensitivity analyses were performed to evaluate PFS in patient subgroups based on key clinical characteristics (e.g., age, triple-negative MBC status, visceral disease involvement, and disease-free interval from adjuvant treatment), as shown

in Figure 6. Within all four clinical subpopulations, the combination of Avastin with chemotherapy provided benefit, with hazard ratios for PFS that were similar to those for the primary analysis results of each study.

Figure 6
Progression-Free Survival in Key Patient Populations



AVF = Avastin; CI = confidence interval; R1-Cap = RIBBON1, capecitabine comparison; R1-T/Anth = RIBBON1, taxane/anthracycline comparison.

In summary, the results for the primary endpoint of PFS in E2100, AVADO, and RIBBON1 demonstrated that Avastin, when combined with standard

chemotherapy regimens for the first-line treatment of patients with HER2-negative MBC, provided a clinically meaningful and statistically significant benefit over chemotherapy alone. This benefit was seen across all classes of chemotherapy studied (taxane-based, anthracycline-based, and capecitabine chemotherapy) and across all clinically important subgroups based on patient demographics and disease characteristics. The stratified hazard ratio in favor of the Avastin-containing arm ranged from 0.48 to 0.69, with overlapping 95% confidence intervals. Improvements in observed median PFS ranged from 0.9 to 5.5 months, whereas the average difference in PFS ranged from 1.5 to 4.1 months. In all trials, the Kaplan–Meier curves for PFS, the most comprehensive summary of the data, showed clear separation in favor of the Avastin-containing arm.

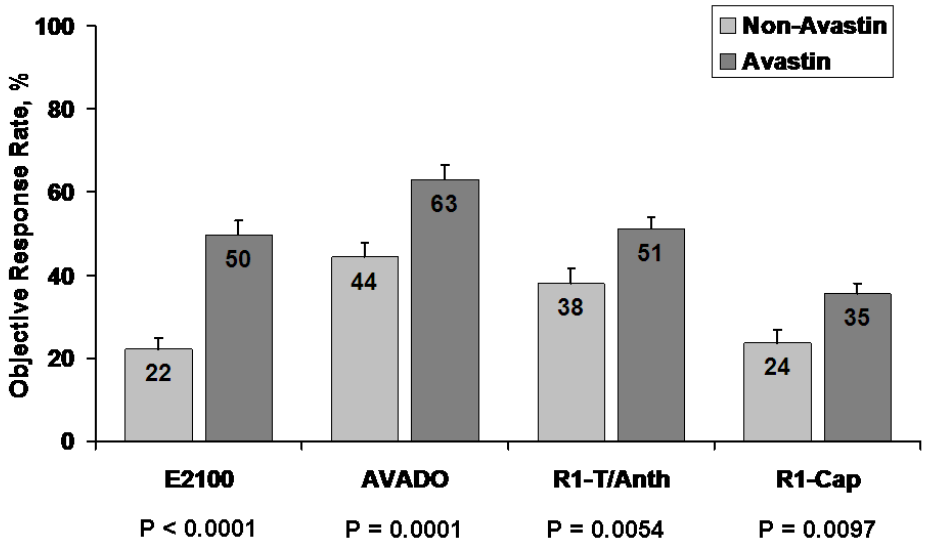
These trials were conducted to ensure that all clinical endpoint measurements were reliably assessed, with the incorporation of a placebo control (AVADO and RIBBON1) and an independent review of PFS (E2100 and RIBBON1). The rate of missing tumor assessment was low and balanced across treatment arms in each study, supporting the reliability of the PFS outcome.

The consistency and reproducibility of PFS benefit with Avastin in combination with commonly used chemotherapies across three Phase III trials with four primary comparisons has been demonstrated.

4.2 OBJECTIVE RESPONSE RATE

Across the three Phase III trials, statistically significant increases in objective response rate (complete responses and partial responses combined) were demonstrated among patients with measurable disease at baseline in the Avastin-containing arms of all three studies (see Figure 7). These increases ranged from 11% to 28% across all efficacy comparisons.

Figure 7
Objective Response Rate in E2100, AVADO, and RIBBON1



R1-Cap = RIBBON1, capecitabine comparison; R1-T/Anth = RIBBON1, taxane/anthracycline comparison.

Median duration of objective response among Avastin-treated patients with measurable disease in all three studies ranged from 7.0 months in AVADO to 9.4 months in E2100. Median duration of objective response among control patients with measurable disease ranged from 6.4 months in AVADO to 9.7 months in E2100.

In conclusion, the combination of Avastin with standard chemotherapy regimens resulted in a statistically significant improvement in objective response rate in patients who had not received chemotherapy for HER2-negative MBC.

4.3 OVERALL SURVIVAL

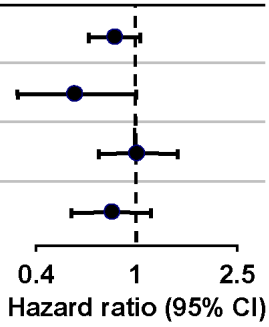
As discussed in Section 2.1, improvements in diagnostic tools and treatment options over the last two decades have resulted in median survival times for MBC patients of approximately 20–24 months (Giordano et al. 2004; Chia et al. 2007). Patients with MBC will typically receive additional lines of treatment after the first line, each of which can mask the survival benefit of the initial treatment line. After completion of first-line therapy, crossover of the control group to the experimental treatment (which was allowed in RIBBON1 and AVADO) confounds measurement of the survival effect of the first-line agents (Mouridsen et al. 2003; Sledge et al. 2003). Many clinical trials in MBC have

failed to show a survival benefit for a specific agent or regimen (see Table 3 in Section 3.3).

Overall survival was included as a secondary outcome measure in all studies. The primary analysis of overall survival for AVADO and RIBBON1 was conducted at the same time as the final PFS analysis, as pre-specified (refer to Appendix F for a description of the methodology). No statistically significant differences were seen in the primary analysis of overall survival (see Figure 8). The hazard ratios for overall survival were similar for all four efficacy comparisons. Although the hazard ratios for E2100 (HR=0.87) and the capecitabine comparison of RIBBON1 (HR=0.85) appear to be more comparable to each other than either the taxane/anthracycline comparison of RIBBON1 (HR=1.03) or AVADO (HR=0.65), the 95% confidence intervals are broadly overlapping.

Figure 8
Primary Analysis of Overall Survival in E2100, AVADO, and RIBBON1

			Non-AVF arm		AVF arm		
Study		N	Event	Median, mo	Event	Median, mo	Hazard ratio (95% CI)
E2100	Pac+AVF vs Pac	722	238	24.8	243	26.5	0.87 (0.72, 1.05)
AVADO	Doc+AVF vs Doc+PL	488	50	-	37	-	0.65 (0.42, 1.02)
R1-T/Anth	T/Anth+AVF vs T/Anth+PL	622	73	23.8	141	25.2	1.03 (0.77, 1.38)
R1-Cap	Cap+AVF vs Cap+PL	615	72	21.2	122	29.0	0.85 (0.63, 1.14)



AVF=Avastin; Cap=capecitabine; CI=confidence interval; Doc=docetaxel; Pac=paclitaxel; PL=placebo; R1-Cap=RIBBON1, capecitabine comparison; R1-T/Anth=RIBBON1, taxane/anthracycline comparison.

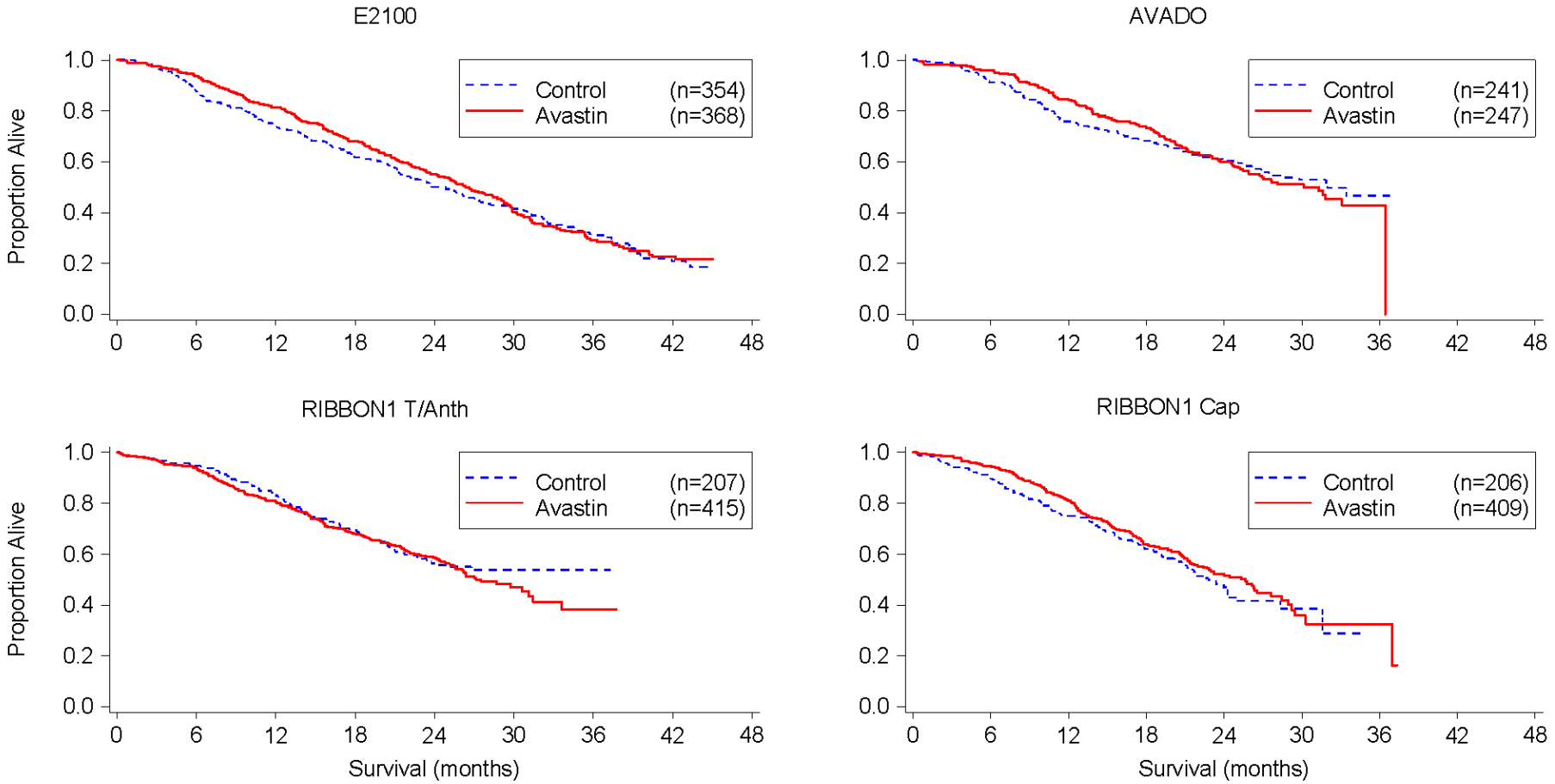
Note: E2100 stratification factors: disease-free interval, prior adjuvant therapy, number of metastatic sites, and estrogen receptor status; AVADO stratification factors: region, prior adjuvant therapy, measurable disease, and hormone receptor status; RIBBON1 stratification factors: disease-free interval, prior adjuvant therapy, number of metastatic sites, and choice of chemotherapy (T/Anth comparison only).

Following unblinding of AVADO and RIBBON1 for the primary efficacy analyses, additional data were available for a planned survival update in these studies (24 months following the “last patient in” for AVADO and 18 months following the “last patient in” for RIBBON1; refer to Appendix F for a description of the

methodology). Kaplan–Meier estimates based on the updated analysis of E2100 and AVADO and the capecitabine comparison of RIBBON1 showed an early separation of the overall survival curves in favor of the Avastin-containing arm (see Figure 9). For the taxane/anthracycline comparison of RIBBON1, the Kaplan–Meier curves showed no difference between treatment arms at any time point. In the updated analysis, the hazard ratios for overall survival were similar for the Avastin-containing and control arms for all efficacy comparisons (see Figure 10). The hazard ratios showed some increases over the earlier values for AVADO (HR = 1.00) and the taxane/anthracycline comparison of RIBBON1 (HR = 1.11). Results for the capecitabine comparison of RIBBON1 were similar to those for the primary analysis (HR = 0.88). The 95% confidence intervals remained overlapping.

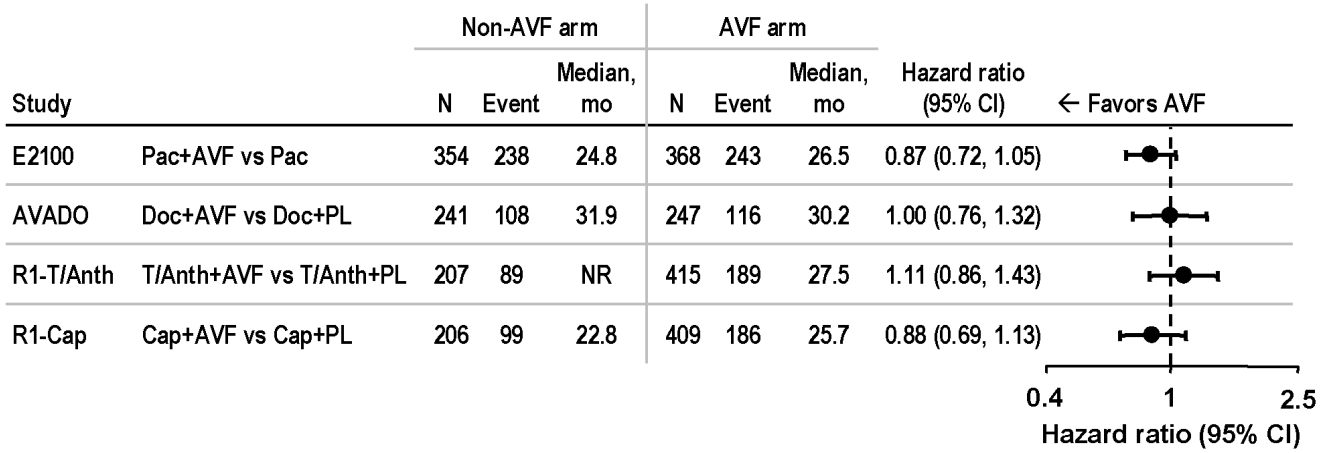
Figure 9

Kaplan–Meier Curves of Overall Survival Based on the Updated Analysis: E2100, AVADO, and RIBBON1



RIBBON1 Cap = capecitabine comparison of RIBBON1; RIBBON1 T/Anth = taxane/anthracycline comparison of RIBBON1.

Figure 10
Updated Analysis of Overall Survival in E2100, AVADO, and RIBBON1



AVF = Avastin; Cap = capecitabine; CI = confidence interval; Doc = docetaxel; Pac = paclitaxel; PL = placebo; R1-Cap = RIBBON1, capecitabine comparison; R1-T/Anth = RIBBON1, taxane/anthracycline comparison.

Several exploratory and sensitivity analyses were performed on the overall survival data from all three studies (refer to Appendix F for a description of the methodology for all analyses described below). A pre-specified exploratory analysis of the taxane subgroup of RIBBON1 revealed a hazard ratio of 1.24 (95% CI: 0.87, 1.77) favoring the taxane + placebo arm. This outcome for RIBBON1 seems to be primarily due to a hazard ratio of 1.45 in the docetaxel subgroup (which contained 181 patients in the intent-to-treat population), as the hazard ratio for the nab-paclitaxel subgroup was 1.05. To further evaluate the results for the docetaxel subgroup of RIBBON1, analyses of patient demographics, disease characteristics, adverse events, serious adverse events, causes of death, overall survival results in key clinical subgroups, and use of subsequent lines of therapy were conducted. No clear clinical explanation was revealed. The results for the docetaxel subgroup of RIBBON1 likely do not represent the true effect of Avastin on overall survival for these patients. They may be due to the small sample size of the docetaxel subgroup of RIBBON1 (n = 181), especially in the placebo arm (n = 58) as a result of the 2:1 randomization scheme. The results from AVADO are considered to be the primary evaluation of the docetaxel + Avastin regimen (intent-to-treat population n = 736) and are not supportive of the RIBBON1 findings.

In all trials, median overall survival was more than double median PFS. Specifically, median survival ranged from 22.8 to 31.9 months in all treatment arms,

whereas median PFS ranged from 5.5 to 11.3 months. This implies that many patients completed or discontinued study treatment well before death. As shown in Table 9, most patients in AVADO and RIBBON1 received some form of second-line and subsequent treatment (note that these data were not collected in E2100). This extensive use of subsequent therapy at investigator discretion may have affected later survival, making it more difficult to assess the effect of Avastin on overall survival in the first-line HER2-negative MBC setting.

Table 9

Percentage of Patients Receiving Second-Line Therapy in AVADO and RIBBON1

			RIBBON1			
	AVADO		T/Anth Comparison		Cap Comparison	
	Doc + Placebo (n = 241)	Doc + Avastin (n = 247)	T/Anth + Placebo (n = 207)	T/Anth + Avastin (n = 415)	Cap + Placebo (n = 206)	Cap + Avastin (n = 409)
Subsequent anti-cancer therapy	83%	82%	82%	75%	77%	75%
Chemotherapy	71%	71%	66%	59%	75%	67%
Avastin	31%	22%	53%	41%	62%	50%
Hormonal therapy	27%	26%	30%	27%	17%	16%
Radiation	10%	7%	18%	12%	9%	12%
Surgery	0%	0%	4%	4%	2%	1%
Other	1%	4%	4%	6%	4%	4%

Cap = capecitabine; Doc = docetaxel; T/Anth = taxane/anthracycline.

4.4 ONE-YEAR SURVIVAL

One-year survival was a secondary endpoint in AVADO and RIBBON1, but not in E2100 (refer to Appendix F for a description of the methodology). As would be expected from review of the Kaplan–Meier curves, in both AVADO and E2100, a higher percentage of patients were alive at 1 year in the Avastin-containing arm than in the control arm (see Table 10). For E2100, the landmark survival analyses demonstrated an improvement in 1-year survival in the paclitaxel + Avastin arm (81%) compared with the paclitaxel-alone arm (74%). Similarly, in AVADO, the 1-year survival rate also showed an improvement in the docetaxel + Avastin arm (84%) compared with the docetaxel + placebo arm (76%) for the updated analysis. For the taxane/anthracycline comparison of RIBBON1, the Kaplan–Meier curves for

the updated analysis showed no difference between treatment arms at any time point, and there was no observed difference in 1-year survival rates (81% vs. 83%). For the capecitabine comparison of RIBBON1, the Kaplan–Meier curves showed an early separation that corresponded to a higher 1-year survival rate in the capecitabine + Avastin arm (81%) compared with the capecitabine + placebo arm (75%) for the updated analysis.

Table 10
One-Year Survival for Individual Studies

	Control Arm Arm	Avastin-Containing Arm	Between-Arm Difference (95% CI)
E2100	74.0%	81.4%	7.4% (1.3%, 13.5%)
AVADO	75.8%	84.3%	8.5% (1.3%, 15.6%)
R1-T/Anth	83.2%	80.7%	−2.6% (−9.0%, 3.9%)
R1-Cap	74.8%	81.0%	6.2% (−1.0%, 13.4%)

CI = confidence interval; R1-Cap = RIBBON1, capecitabine comparison;
R1-T/Anth = RIBBON1, taxane/anthracycline comparison.

4.5 HEALTH-RELATED QUALITY OF LIFE

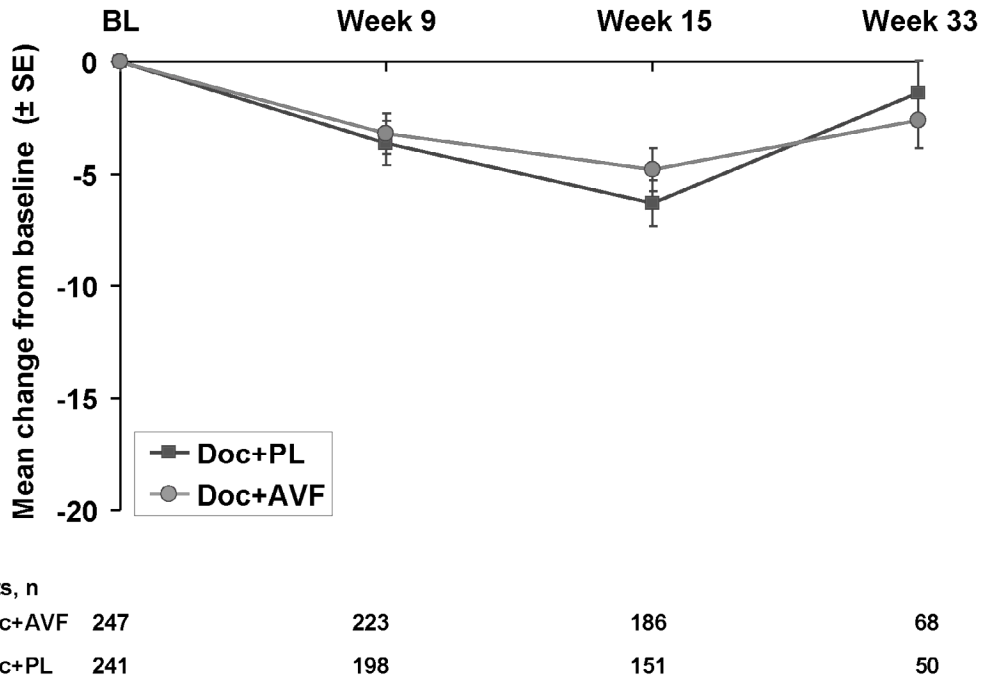
E2100 and AVADO used the Functional Assessment of Cancer Therapy—Breast (FACT-B, v4) instrument to capture health-related quality-of-life (HRQOL) assessments at baseline and during follow-up.

The FACT-B 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 subscale (BCS). In the double-blind study AVADO, the FACT-B was administered to patients at baseline, Week 9 (Cycle 3), Week 15 (Cycle 5), and Week 33 (Cycle 11) while they were on treatment. The Trial Outcome Index (TOI), which includes the sum of PWB, FWB, and BCS, and the FACT-B total score (sum of all five subscales), was calculated for each patient at each evaluation.

There was good compliance with the HRQOL assessments in AVADO, with at least 85% of on study patients completing their HRQOL questionnaire. The mean TOI scores and FACT-B total scores were similar between treatment arms at baseline. The mean change from baseline in TOI and FACT-B total scores was not statistically different between treatment arms, supporting the finding that treatment with the combination of Avastin and chemotherapy did not appear to affect patients' HRQOL

any more than chemotherapy alone and no detriment to HRQOL was observed in this study (see Figure 11 for the mean change in TOI scores over time).

Figure 11
Health-Related Quality-of-Life Analyses for AVADO: Trial Outcome Index of the FACT-B Instrument



AVF = Avastin 15 mg/kg every 3 weeks; BL = baseline; Doc = docetaxel; PL = placebo; SE = standard error.

HRQOL was assessed in a similar manner in the open-label study E2100, and the results were comparable (Miller et al. 2007). In both trials, patients receiving chemotherapy had a slight decline in FACT-B scores during treatment. In E2100 and AVADO, chemotherapy appeared to negatively affect patients' HRQOL, as has been reported in other studies (E1193; Sledge et al. 2003). Because Avastin was given in combination with chemotherapy, it is not surprising that there was no improvement, on average, in HRQOL, since patients continued to experience side effects from chemotherapy. In AVADO, there is a slight increase in TOI scores at Week 33 from Week 15, possibly because patients' chemotherapy treatment was stopped at around Week 27 (Cycle 9) per protocol. The results support the conclusion that treatment with the combination of Avastin and the standard chemotherapy regimens used in each trial did not negatively affect patients' HRQOL,

despite the longer time on treatment, and therefore Avastin did not add to the burden of receiving cytotoxic chemotherapy.

In summary, the available HRQOL data from trials combining Avastin with the taxanes paclitaxel and docetaxel suggest that Avastin did not lead to an increase in the treatment burden experienced by these patients.

4.6 SAFETY PROFILE OF AVASTIN IN THE FIRST-LINE MBC SETTING

Avastin has a well-characterized safety profile when used in combination with other agents or as monotherapy, depending on the approved indication (colorectal cancer, non-squamous non–small cell lung cancer, MBC, glioblastoma, and renal cell cancer). Because Avastin is approved for the treatment of multiple cancer types and a broad development plan is ongoing, we now have safety data from over 6 years of postmarketing experience, which includes more than 812,000 patients exposed to marketed product and in clinical trials. Adverse events associated with Avastin treatment include commonly recognized events, such as hypertension or proteinuria, and less common, severe adverse events, which occur at a low incidence (e.g., gastrointestinal [GI] perforation, arterial thromboembolic [ATE] events, congestive heart failure, reversible posterior leukoencephalopathy syndrome [RPLS], venous thromboembolic [VTE] events, and higher grade bleeding).

All safety data from the three Phase III trials, including the 7.5 mg/kg arm of AVADO, were reviewed for a comprehensive evaluation of Avastin safety. The pooled analysis of safety includes 2661 safety-evaluable patients: 711 patients in E2100, 730 patients in AVADO, and 1220 patients in RIBBON1.

Drug Exposure

Avastin exposure, taxane exposure, and capecitabine exposure varied moderately across studies as the result of differences in study design and patient population. Because E2100 had the longest median PFS in the paclitaxel + Avastin arm, it also had the longest median taxane exposure and median Avastin exposure of the taxane studies (see Table 11). The median duration of chemotherapy was longer in Avastin-treated patients than in control patients in all studies, with the exception of the taxane-treated patients in RIBBON1, for whom the durations were similar. This indicates that the addition of Avastin did not compromise the delivery of chemotherapy.

Table 11
Chemotherapy Treatment Duration

	E2100		AVADO			RIBBON1 T/Anth Comparison		RIBBON1 T/Anth Comparison		RIBBON1 Cap Comparison	
	Pac (n=348)	Pac+ Avastin (n=363)	Doc+ Placebo (n=231)	Doc+ Avastin7.5 (n=252)	Doc+ Avastin (n=247)	T+ Placebo (n=102)	T+ Avastin (n=203)	Anth+ Placebo (n=100)	Anth+ Avastin (n=210)	Cap+ Placebo (n=201)	Cap+ Avastin (n=404)
n	342	358	231	252	246	102	203	100	209	201	404
Mean (SD)	5.9 (4.6)	8.5 (5.6)	4.3 (1.6)	4.5 (1.6)	4.6 (1.6)	5.5 (4.4)	5.6 (4.7)	4.0 (2.5)	4.7 (3.3)	6.0 (5.7)	7.4 (6.1)
Median (range)	5.1 (0.0–25.4)	7.3 (0.0–30.1)	4.9 (0.0–6.7)	5.1 (0.0–7.3)	5.5 (0.0–8.1)	4.7 (0.0–30.5)	4.4 (0.0–29.0)	3.5 (0.0–15.4)	3.9 (0.0–22.8)	3.7 (0.0–24.6)	5.7 (0.0–30.7)

Anth=anthracycline; Cap=capecitabine; Doc=docetaxel; Pac=paclitaxel; T=taxane; T/Anth=taxane/anthracycline.

Note: Patients in the Doc+Avastin7.5 arm of AVADO received Avastin 7.5 mg/kg every 3 weeks; all other Avastin-treated patients received an Avastin dose of either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks until disease progression or toxicity.

Adverse Events

On the basis of the broad safety experience with Avastin, adverse events commonly associated with treatment have been identified. These "selected adverse events," such as hypertension, proteinuria, ATE events, GI perforations, VTE events, RPLS, and bleeding, are described in the Avastin® U.S. Package Insert. Table 12 shows the incidence of these selected adverse events in E2100, AVADO, and RIBBON1. Table 13 shows the incidence of Grade ≥3 selected adverse events based on the pooled analysis.

The results indicate that for certain adverse events (e.g., hypertension and proteinuria) Avastin increased the incidence regardless of the chemotherapy background. The incidence of other events varied by chemotherapy; for instance, an increased incidence of febrile neutropenia was associated with the use of taxanes but not capecitabine.

The severity of the most frequent Avastin-associated adverse event, hypertension, was reported as Grade 3 in the majority of patients; 5 patients experienced Grade 4 hypertension.

Table 12

Overview of Safety Results (Grade ≥3 Selected Adverse Events) for Patients in E2100, AVADO, and RIBBON1

	E2100		AVADO			RIBBON1					
						T/Anth Comparison		T/Anth Comparison		Cap Comparison	
	Pac (n=348)	Pac+ Avastin (n=363)	Doc+ Placebo (n=231)	Doc+ Avastin7.5 (n=252)	Doc+ Avastin (n=247)	T+ Placebo (n=102)	T+ Avastin (n=203)	Anth+ Placebo (n=100)	Anth+ Avastin (n=210)	Cap+ Placebo (n=201)	Cap+ Avastin (n=404)
Any Grade ≥3 selected adverse event	89 (25.6%)	180 (49.6%)	87 (37.7%)	108 (42.9%)	112 (45.3%)	23 (22.5%)	89 (43.8%)	11 (11.0%)	51 (24.3%)	17 (8.5%)	87 (21.5%)
Arterial thromboembolic event	0 (0.0%)	13 (3.6%)	1 (0.4%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	3 (1.4%)	2 (1.0%)	8 (2.0%)
Bleeding	1 (0.3%)	8 (2.2%)	2 (0.9%)	3 (1.2%)	3 (1.2%)	0 (0.0%)	11 (5.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.2%)
Febrile neutropenia	0 (0.0%)	6 (1.7%)	27 (11.7%)	38 (15.1%)	41 (16.6%)	2 (2.0%)	16 (7.9%)	5 (5.0%)	8 (3.8%)	0 (0.0%)	0 (0.0%)
GI perforation	0 (0.0%)	2 (0.6%)	2 (0.9%)	1 (0.4%)	1 (0.4%)	1 (1.0%)	4 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	5 (1.4%)	58 (16.0%)	3 (1.3%)	2 (0.8%)	11 (4.5%)	2 (2.0%)	19 (9.4%)	0 (0.0%)	21 (10.0%)	2 (1.0%)	40 (9.9%)
LVSD	1 (0.3%)	8 (2.2%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	4 (2.0%)	0 (0.0%)	6 (2.9%)	1 (0.5%)	4 (1.0%)
Neutropenia	14 (4.0%)	29 (8.0%)	45 (19.5%)	54 (21.4%)	52 (21.1%)	5 (4.9%)	19 (9.4%)	4 (4.0%)	9 (4.3%)	2 (1.0%)	5 (1.2%)
Proteinuria	0 (0.0%)	11 (3.0%)	0 (0.0%)	2 (0.8%)	5 (2.0%)	0 (0.0%)	8 (3.9%)	0 (0.0%)	4 (1.9%)	0 (0.0%)	9 (2.2%)
RPLS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sensory neuropathy	63 (18.1%)	90 (24.8%)	10 (4.3%)	20 (7.9%)	19 (7.7%)	9 (8.8%)	17 (8.4%)	0 (0.0%	1 (0.5%)	1 (0.5%)	12 (3.0%)
Venous thromboembolic event	15 (4.3%)	11 (3.0%)	8 (3.5%)	4 (1.6%)	3 (1.2%)	5 (4.9%)	4 (2.0%)	2 (2.0%)	6 (2.9%)	7 (3.5%)	19 (4.7%)

Anth=anthracycline; Cap=capecitabine; Doc=docetaxel; GI=gastrointestinal; LVSD=left ventricular systolic dysfunction; Pac=paclitaxel; RPLS=reversible posterior leukoencephalopathy syndrome; T=taxane; T/Anth=taxane/anthracycline.

Note: Patients in the Doc+Avastin7.5 arm of AVADO received Avastin 7.5 mg/kg every 3 weeks; all other Avastin-treated patients received an Avastin dose of either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks until disease progression or toxicity.

Table 13
Pooled Analysis of Grade ≥3 Selected Adverse Events
in Patients Treated in the First-Line Setting

	Pooled Results	
	Chemotherapy (n=982)	Chemotherapy + Avastin (n=1679)
Any Grade ≥3 selected adverse event	227 (23.1%)	627 (37.3%)
Arterial thromboembolic event	3 (0.3%)	27 (1.6%)
Bleeding	4 (0.4%)	26 (1.5%)
Febrile neutropenia	34 (3.5%)	109 (6.5%)
Fistula	3 (0.3%)	8 (0.5%)
GI perforation	3 (0.3%)	8 (0.5%)
Hypertension	12 (1.2%)	151 (9.0%)
LVSD	2 (0.2%)	25 (1.5%)
Neutropenia	70 (7.1%)	168 (10.0%)
Proteinuria	0 (0.0%)	39 (2.3%)
RPLS	0 (0.0%)	1 (<0.1%)
Sensory neuropathy	83 (8.5%)	159 (9.5%)
Venous thromboembolic event	37 (3.8%)	47 (2.8%)

GI=gastrointestinal; LVSD=left ventricular systolic dysfunction; RPLS=reversible posterior leukoencephalopathy syndrome.

Across the studies (see Table 12) and in the pooled analyses (see Table 13), the incidence of adverse events commonly associated with Avastin (e.g., hypertension, proteinuria, ATE events, GI perforations, VTE events, RPLS, and bleeding) was consistent with previous Avastin experience (see Table 14). The combination of Avastin with specific chemotherapy regimens did not result in a marked increase in the incidence of adverse events associated with those regimens (e.g., neutropenia and sensory neuropathy with taxanes), which is consistent with the non-overlapping toxicities between Avastin and cytotoxic agents.

Table 14 compares the incidences of selected adverse events based on the pooled analysis with those reported in the Avastin® U.S. Package Insert.

Table 14
Incidence of Selected Adverse Events Based on the Avastin® U.S. Package Insert and the Pooled Analysis of Results from E2100, AVADO, and RIBBON1

	Incidence of Selected Adverse Events	
	Per the Avastin® U.S. Package Insert	Per the Pooled Analysis
Warnings and precautions		
GI perforation	0.3%–2.4%	0.5%
Hemorrhage	1.2%–4.6%	1.5%
Arterial thromboembolic events	2.4%	1.6%
Hypertension	5%–18%	9.0%
Proteinuria	0.7%–7.4%	2.3%
Adverse reactions		
Venous thromboembolic events	15.11%	2.8%
Neutropenia and infection		
Febrile neutropenia	5.42%	6.5%
Neutropenia	26.22%	10.0%
Congestive heart failure (LVSD)	3.83%	1.5%

GI = gastrointestinal; LSVD = left ventricular systolic dysfunction.

As shown in Table 14, safety data from patients in the three Phase III trials demonstrated that the adverse events reported in patients with MBC treated in the first-line setting were consistent with the well-characterized profile described in the Avastin® U.S. Package Insert. The incidence of common adverse events associated with Avastin treatment (e.g., hypertension, low-grade bleeding, and proteinuria) was consistent with that seen in previous Avastin studies. These events could be managed with clinical interventions consistent with clinical practice. The well-characterized adverse events associated with Avastin that are potentially more significant, such as ATE events, GI perforations, congestive heart failure, VTE events, RPLS, and higher grade bleeding, occurred at a low incidence across the three studies and in the pooled analysis. No new or unexpected safety signals were observed in E2100, AVADO, or RIBBON1.

Across studies and in the pooled analysis, the incidence and management of adverse events associated with the specific chemotherapy regimens (e.g., neutropenia and sensory neuropathy) were consistent with previous clinical experience. The increases observed in chemotherapy-associated adverse events

with the addition of Avastin did not substantially impact the usage of first-line chemotherapy. This was evidenced by the generally longer duration of exposure and comparable dose intensity for the chemotherapy backbone in the Avastin-containing arms relative to the control arms. No age-related imbalances were noted. The incidence of safety events associated with a specific chemotherapy regimen (e.g., neutropenia and sensory neuropathy) was not increased to an extent that would change the clinical decision to use that chemotherapy.

Table 15 shows the rate of study drug (Avastin or placebo) discontinuation due to an adverse event in patients who received taxane therapy in AVADO or RIBBON1. Adverse events that led to study drug discontinuation were not collected in E2100. The rates of study drug discontinuation ranged from 8.7% to 25.1%, which is comparable to rates observed in other Phase III MBC studies with chemotherapy (Jones et al. 2005; Thomas et al. 2007; Di Leo et al. 2008; Chan et al. 2009). No single adverse event or adverse events in a system organ class, including those that are specific to taxane therapy, were predominantly responsible for study drug discontinuation in any of the taxane-containing arms.

Table 15

Adverse Events Occurring at a ≥2% Incidence and Requiring Avastin or Placebo Discontinuation in Patients Who Received Taxane Therapy

	AVADO			RIBBON1	
Preferred Term	Doc+Placebo (n=231)	Doc+Avastin7.5 (n=252)	Doc+Avastin (n=247)	T+Placebo (n=102)	T+Avastin (n=203)
Any adverse event	27 (11.7%)	22 (8.7%)	34 (13.8%)	9 (8.8%)	51 (25.1%)
Deep vein thrombosis	1 (0.4%)	(0.0%)	(0.0%)	2 (2.0%)	(0.0%)
GI perforation	(0.0%)	(0.0%)	(0.0%)	(0.0%)	5 (2.5%)
Hypertension	(0.0%)	(0.0%)	3 (1.2%)	(0.0%)	5 (2.5%)
Proteinuria	(0.0%)	(0.0%)	4 (1.6%)	(0.0%)	4 (2.0%)

Doc=docetaxel; GI=gastrointestinal; T=taxane.

Note: Patients in the Doc+Avastin7.5 arm of AVADO received Avastin 7.5 mg/kg every 3 weeks; all other Avastin-treated patients received an Avastin dose of 15 mg/kg every 3 weeks until disease progression or toxicity.

There was an increase in the incidence of adverse events leading to study drug discontinuation in the anthracycline+Avastin arm compared with the anthracycline+placebo arm (15.2% vs. 4.0%). The only adverse event leading to blinded study drug discontinuation with a ≥2% difference in incidence between the two treatment arms was hypertension (2.9% in the anthracycline+Avastin arm

vs. 0.0% in the anthracycline + placebo arm). No other single adverse event or adverse events in a system organ class, including those that are specific to anthracyclines, were predominantly responsible for study drug discontinuation in the anthracycline + Avastin arm.

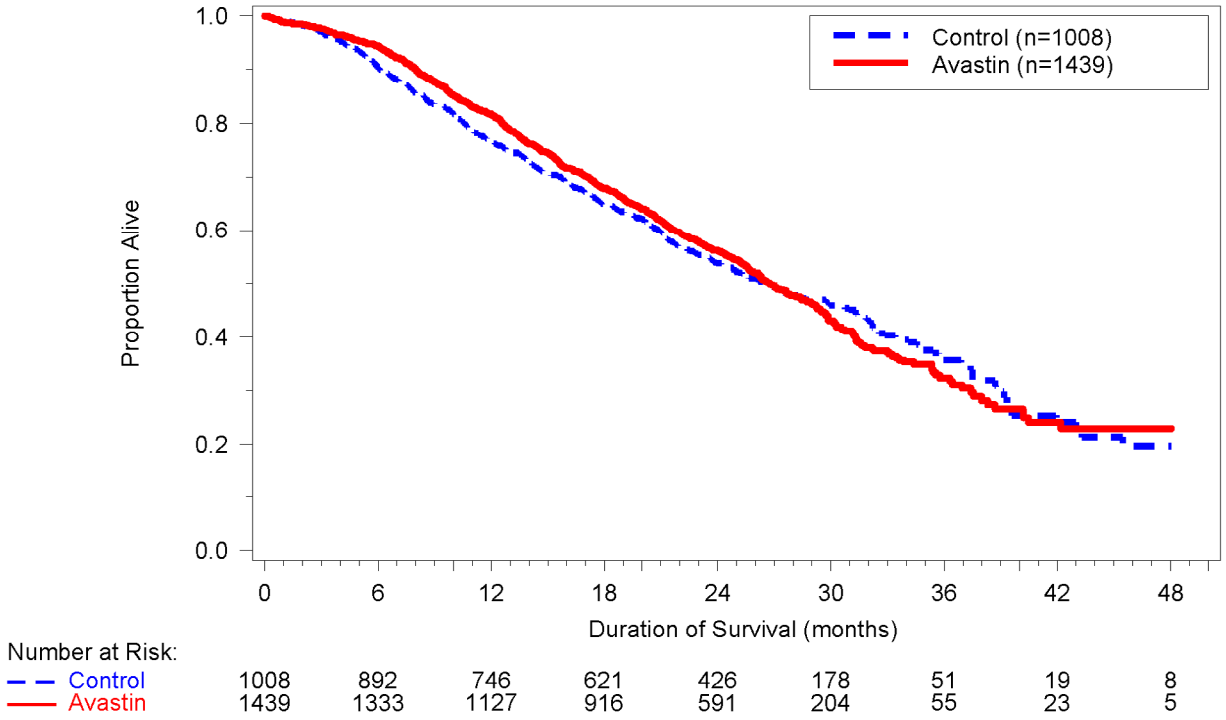
The incidence of adverse events leading to discontinuation of study drug was similar in the capecitabine + Avastin and capecitabine + placebo arms of RIBBON1 (12.6% vs. 11.9%, respectively). No single adverse event or adverse events in a system organ class, including those that are specific to capecitabine, were predominantly responsible for study drug discontinuation in the capecitabine + Avastin arm.

To summarize the adverse event profile, data from three Phase III trials, enrolling approximately 2700 patients, resulted in an adverse event profile that was consistent across the three studies and with that previously observed in clinical trials of Avastin in other tumor types and described in the Avastin® U.S. Package Insert. Common adverse events associated with Avastin treatment (e.g., hypertension and proteinuria) differ from those associated with chemotherapy. There was a low incidence of severe safety events that are known to be associated with the combination of Avastin and chemotherapy (e.g., ATE events, GI perforations, and severe bleeding). Therefore, the data from E2100, AVADO, and RIBBON1 complement and are consistent with the comprehensive body of safety data for Avastin across multiple tumor types.

Deaths (Including Treatment-Related Deaths)

In accordance with the discussion in Section 3.4 regarding the criteria for conversion of the accelerated approval, Genentech has concluded that there was no impairment of overall survival in E2100, AVADO, or RIBBON1. As part of this assessment, an exploratory, pooled analysis of overall survival across the three studies was performed (refer to Appendix F for a description of the methodology). Each individual study was used as the stratification factor in the stratified analysis. The estimated hazard ratio for overall survival based on the pooled analysis was 0.97 (95% CI: 0.86, 1.08; log-rank $p = 0.56$), and median overall survival was similar in the Avastin-containing arm (26.7 months) and the control arm (26.4 months). As such, results from comprehensive analyses of all three studies and from the pooled analysis of overall survival demonstrated that treatment with Avastin in combination with first-line chemotherapy did not impair overall survival.

Figure 12
Kaplan–Meier Curves for the Pooled Analysis of Updated Overall Survival: E2100, AVADO, and RIBBON1



Number at Risk:

Control	1008	892	746	621	426	178	51	19	8
Avastin	1439	1333	1127	916	591	204	55	23	5

To further support a lack of impairment of overall survival, treatment-related deaths were assessed. An imbalance in the incidence of treatment-related death was previously noted for the open-label study E2100, in which the incidence in the control arm was notably lower than that in the control arms of the other studies (see Table 16). No specific adverse event contributed to deaths in the Avastin-containing arm of E2100: two deaths were due to myocardial infarction, one death was due to GI perforation, and one death was due to respiratory failure. The imbalance in events could be due to the manner in which safety data were collected in E2100 (more safety data were collected for the Avastin-containing arm than for the control arm). The combination of Avastin with taxane-based, anthracycline-based, or capecitabine chemotherapy did not increase the incidence of deaths unrelated to disease progression relative to the respective control arm in the two double-blind studies (AVADO and RIBBON1).

Table 16
Cause of Death in E2100, AVADO, and RIBBON1

	E2100		AVADO			RIBBON1 T/Anth Comparison		RIBBON1 T/Anth Comparison		RIBBON1 Cap Comparison	
	Pac (n=348)	Pac+ Avastin (n=363)	Doc+ Placebo (n=231)	Doc+ Avastin7.5 (n=252)	Doc+ Avastin (n=247)	T+ Placebo (n=102)	T+ Avastin (n=203)	Anth+ Placebo (n=100)	Anth+ Avastin (n=210)	Cap+ Placebo (n=201)	Cap+ Avastin (n=404)
Deaths	257	256	106	120	114	44	101	44	86	97	185
MBC	241 (69.3%)	241 (66.4%)	98 (42.4%)	110 (43.7%)	107 (43.3%)	38 (37.3%)	90 (44.3%)	40 (40.0%)	82 (39.0%)	89 (44.3%)	166 (41.1%)
AE or protocol therapy	1 (0.3%)	6 (1.7%)	6 (2.6%)	9 (3.6%)	7 (2.8%)	3 (2.9%)	5 (2.5%)	3 (3.0%)	2 (1.0%)	5 (2.5%)	6 (1.5%)
Other	7 (2.0%)	5 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.9%)	6 (3.0%)	1 (1.0%)	2 (1.0%)	3 (1.5%)	13 (3.2%)
Missing/ unknown cause	8 (2.3%)	4 (1.1%)	2 (0.9%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

AE=adverse event; Anth=anthracycline; Cap=capecitabine; Doc=docetaxel; MBC=metastatic breast cancer; Pac=paclitaxel; T=taxane; T/Anth=taxane/anthracycline.

Note: Patients in the Doc+Avastin7.5 arm of AVADO received Avastin 7.5 mg/kg every 3 weeks; all other Avastin-treated patients received an Avastin dose of either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks until disease progression or toxicity.

Across studies, the difference in the proportion of patients who died as the result of MBC can be accounted for by the respective difference in follow-up. E2100 had the longest follow-up and consequently had the highest observed incidence of death due to MBC. Deaths due to an adverse event or protocol therapy constituted a small percentage of the overall deaths in all studies. In E2100, the open-label control arm had the lowest incidence of death due to an adverse event or protocol therapy of any taxane-containing arm in the three studies, whereas the Avastin-containing arm of E2100 had an incidence of death consistent with that in the taxane-containing arms of AVADO and RIBBON1, regardless of Avastin exposure.

Results from the pooled analysis of E2100, AVADO, and RIBBON1 showed a similar incidence of treatment-related deaths in patients who received Avastin in combination with chemotherapy and in those who received chemotherapy alone: the incidence of treatment-related death was 2.1% in the Avastin-containing arm, compared with 1.8% in the control arm (see Table 17). The primary cause of death in both treatment arms was MBC.

Table 17
Cause of Death: Pooled Analysis of Patients Treated in the First-Line Setting

	Pooled Results	
	Chemotherapy (n = 982)	Chemotherapy + Avastin (n = 1679)
Deaths	548	862
MBC	506 (51.5%)	796 (47.4%)
Adverse event or protocol therapy	18 (1.8%)	35 (2.1%)
Other	14 (1.4%)	26 (1.5%)
Missing/unknown cause	10 (1.0%)	5 (0.3%)

MBC = metastatic breast cancer.

As further due diligence, for every death reported in the clinical trial database, a clinical review of all available data was performed to confirm the cause of death and rule out possible treatment-related mortality. As expected, the large majority of deaths resulted from underlying MBC, consistent with the results in Table 17. Additionally, the clinical review confirmed that no specific adverse event or

adverse events in a particular organ system led to the treatment-related deaths observed in the studies.

Therefore, across these three studies, the data and clinical review confirmed that treatment with the combination of Avastin and chemotherapy did not result in an increase in treatment-related deaths. Additionally, the pooled analysis demonstrates no difference between treatment arms in overall survival and provides a more precise estimate of survival (stratified HR = 0.97; 95% CI: 0.86, 1.08; log-rank p = 0.56). In conclusion, treatment with the combination of Avastin and chemotherapy did not result in an increase in treatment-related deaths, and there was no impairment of overall survival in the studies of Avastin as first-line treatment for patients with HER2-negative MBC (E2100, AVADO, and RIBBON1).

4.7 SUMMARY AND DISCUSSION OF AVASTIN DATA TO SUPPORT CONVERSION TO FULL APPROVAL

Three Phase III, controlled clinical trials of Avastin have been conducted using multiple classes of chemotherapeutic agents, including taxanes, anthracyclines, and capecitabine, in over 2400 women with HER2-negative MBC. These data demonstrate the following:

- The combination of Avastin with first-line chemotherapy consistently and reliably improved the time women lived with this incurable cancer under control, compared with chemotherapy alone.
- In the first-line MBC setting, the safety profile of Avastin was consistent with that reported in the Avastin® U.S. Package Insert.
- Avastin could be safely and effectively combined with commonly used chemotherapeutic agents, beyond paclitaxel, providing physicians with multiple therapeutic options to address individual patient needs.

Genentech has provided data that meet the criteria for conversion of the accelerated approval to full approval according to the criteria agreed upon with the FDA. More importantly, the consistent and reliable prolongation of disease control across these studies, supported by increases in the number of objective responses and the tolerable and well-characterized safety profile, constitutes clinically meaningful benefit. The totality of data demonstrates a clinically significant improvement in PFS that is reliable and robust, with no impairment of overall survival. Avastin in combination with chemotherapy is an important first-line treatment for women with HER2-negative MBC.

5. BENEFIT–RISK ASSESSMENT FOR AVASTIN BY CHEMOTHERAPY COMBINATION

All three studies, incorporating various chemotherapy backbones, demonstrated similar efficacy and safety findings:

- Consistent results showing that the combination of Avastin with chemotherapy led to a statistically significant and clinically meaningful improvement in PFS compared with chemotherapy alone
- Increased objective response rates with the combination of Avastin with various chemotherapies, regardless of the control objective response rate
- No impairment of overall survival, as shown in the individual studies
- Minimal impact on HRQOL was seen when Avastin was combined with taxane therapy.
- A consistent adverse event profile for MBC patients, which is similar to the experience in other tumor indications
- No substantial increase in the incidence of the known toxicities of the chemotherapy partner or limitation of its delivery owing to the addition of Avastin

The following sections provide a comprehensive discussion of the benefit–risk profile for Avastin in combination with each of the specific chemotherapy regimens evaluated in the three studies and proposed in the draft label.

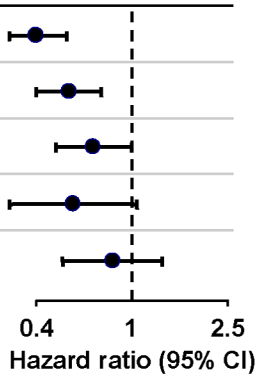
5.1 TAXANES IN COMBINATION WITH AVASTIN

A total of 818 patients were treated with Avastin in combination with a taxane in the three Phase III trials: E2100 (paclitaxel; n=368), AVADO (docetaxel; n=247 in the 15 mg/kg arm), and RIBBON1 (docetaxel and nab-paclitaxel; n=203). Results from all three trials demonstrated persuasive and clinically meaningful improvement in disease control when Avastin was combined with this important class of chemotherapeutic agents commonly used to treat patients with breast cancer. Results from the three trials also demonstrated that the safety profile for this combination was consistent with previous Avastin experience (in MBC, in other indications, and as described in the Avastin® U.S. Package Insert) and that the additional treatment burden associated with Avastin was manageable and did not substantially increase taxane-associated toxicity. These data support a positive benefit–risk assessment for the use of Avastin in combination with taxane-based chemotherapy as first-line treatment of patients with HER2-negative MBC.

Figure 13 presents the PFS results for all taxane-treated patients, which indicated a consistent treatment effect in all trials, with broadly overlapping confidence intervals.

Figure 13
PFS among Taxane-Treated Patients in E2100, AVADO, and RIBBON1

		Non-AVF arm			AVF arm		
Study		N	Event	Median, mo	Event	Median, mo	Hazard ratio (95% CI)
E2100	Pac+AVF vs Pac	722	184	5.8	173	11.3	0.48 (0.39, 0.61)
AVADO	Doc+AVF vs Doc+PL	488	152	7.9	134	8.8	0.62 (0.48, 0.79)
R1-T/Anth	T/Anth+AVF vs T/Anth+PL	307	79	8.2	125	9.2	0.75 (0.56, 1.01)
	Abr+AVF vs Abr+PL	124	32	6.7	46	9.6	0.64 (0.39, 1.05)
	Doc+AVF vs Doc+PL	181	47	8.4	78	9.2	0.87 (0.59, 1.27)



Abr = nab-paclitaxel; AVF = Avastin; CI = confidence interval; Doc = docetaxel; Pac = paclitaxel; PL = placebo; R1-T/Anth = RIBBON1, taxane/anthracycline comparison.

Further discussion regarding the benefit–risk assessment of each taxane agent (paclitaxel, nab-paclitaxel, and docetaxel) is provided below.

5.1.1 Paclitaxel and Nab-Paclitaxel in Combination with Avastin

Paclitaxel and nab-paclitaxel share the same active moiety and differ only in formulation. In contrast to paclitaxel, which includes polyethylated castor oil as a solvent, nab-paclitaxel is a biologically interactive, nanometer-sized albumin-bound paclitaxel particle that was initially developed to increase efficacy and minimize the toxicities associated with standard paclitaxel therapy.
Data from the Phase III trial ABI-007 demonstrated efficacy for nab-paclitaxel that was comparable to that of paclitaxel in MBC (as measured by objective response rate and TTP) and favorable safety (Gradishar et al. 2005). Nab-paclitaxel was approved as Abraxane® by the FDA under the 505(b)(2) regulations of the Federal Food, Drug and Cosmetic Act , which recognized that nab-paclitaxel and paclitaxel have the same active ingredient. The FDA granted the same indication for Abraxane® as paclitaxel on the basis of the comparable efficacy demonstrated for the two products (Abraxane Medical Review, Summary Basis

of Approval). As such, paclitaxel and nab-paclitaxel can be considered comparable and are discussed concurrently in this section.

E2100 was a Phase III trial of 722 patients designed to investigate the benefit of combining Avastin with paclitaxel as first-line treatment for patients with HER2-negative MBC. As discussed in Section 4.1, this study demonstrated that the combination of Avastin with paclitaxel led to an improvement in PFS (see Table 18). The primary efficacy results were confirmed by a retrospective review conducted by an independent radiology facility and by comprehensive sensitivity analyses.

Within the taxane/anthracycline comparison of RIBBON1, a subgroup of patients received Avastin in combination with nab-paclitaxel (n=78). Despite the small size, results for this subgroup were consistent with the E2100 findings.

Table 18
Efficacy Results for Study E2100 and for Nab-Paclitaxel–Treated Patients in RIBBON1

	E2100		RIBBON1	
	Pac (n=354)	Pac+Avastin (n=368)	Abr+Placebo (n=46)	Abr+Avastin (n=78)
PFS				
Patients with a PFS event	184 (52.0%)	173 (47.0%)	32 (69.6%)	46 (59.0%)
PFS (months)				
HR [a] (relative to placebo) (95% CI)	0.48 (0.39, 0.61)		0.64 (0.39, 1.05)	
Median	5.8	11.3	6.7	9.6
Objective response rate				
Patients with measurable disease	243	229	37	59
Objective response rate	54 (22.2%)	114 (49.8%)	10 (27.0%)	30 (50.8%)
Between-arm difference (95% CI)	27.6% (19.2%, 35.9%)		23.8% (3.1%, 44.6%)	
Overall survival (updated) [b]				
Patients who died	238 (67.2%)	243 (66.0%)	24 (52.2%)	40 (51.3%)
Overall survival (months)				
HR [a] (relative to placebo) (95% CI)	0.87 (0.72, 1.05)		1.05 (0.62, 1.78)	
Median	24.8	26.5	24.9	25.6

Abr=nab-paclitaxel; CI=confidence interval; HR=hazard ratio; Pac=paclitaxel; PFS=progression-free survival.

[a] Stratified analysis.

[b] The cutoff for the updated analysis of overall survival was 23 February 2009 for RIBBON1. Only one analysis (data cutoff of 21 October 2006) was conducted for E2100.

The safety profile seen in E2100 and the nab-paclitaxel subgroup of RIBBON1 was consistent with that seen in other indications and described in the Avastin® U.S. Package Insert. Although there was an increase in treatment-related deaths in E2100, this finding was not replicated in other studies combining Avastin with taxane-based chemotherapy, such as AVADO and RIBBON1, and discussed in Section 4.6.

Table 19 shows the incidence of selected adverse events reported in paclitaxel-treated patients in E2100 and the subgroup of nab-paclitaxel–treated patients in RIBBON1. Adverse events of particular interest in patients treated with paclitaxel include sensory neuropathy, and neutropenia, and febrile neutropenia. As seen in Table 19, an increased incidence of Grade ≥3 sensory neuropathy was observed in the paclitaxel+Avastin arm of E2100 (24.8% vs. 18.1% in the control arm), but not in the nab-paclitaxel+Avastin arm of RIBBON1 (11.3% vs. 18.2% in the control arm). The higher incidence of sensory neuropathy in E2100 likely resulted from the use of weekly paclitaxel rather than an every 3 week schedule. The incidence of sensory neuropathy seen in the nab-paclitaxel–treated patients of RIBBON1 is consistent with reported incidence rates for nab-paclitaxel.

The incidence of Grade 3 neutropenia and febrile neutropenia was also increased in patients who received Avastin in combination with either paclitaxel of nab-paclitaxel. However, these events occurred at a relatively low incidence (<12%) and were manageable, as fewer than 2% of patients discontinued study drug because of neutropenia and febrile neutropenia.

Table 19
Incidence of Grade ≥3 Selected Adverse Events in E2100 and among Patients Treated with Nab-Paclitaxel in RIBBON1

	E2100		RIBBON1	
Selected Adverse Event Category	Pac (n=348)	Pac+Avastin (n=363)	Abr+Placebo (n=44)	Abr+Avastin (n=80)
Any Grade ≥3 selected adverse event	89 (25.6%)	180 (49.6%)	12 (27.3%)	36 (45.0%)
Arterial thromboembolic event	0 (0.0%)	13 (3.6%)	0 (0.0%)	0 (0.0%)
Bleeding	1 (0.3%)	8 (2.2%)	0 (0.0%)	5 (6.3%)
Febrile neutropenia	0 (0.0%)	6 (1.7%)	0 (0.0%)	3 (3.8%)
GI perforation	0 (0.0%)	2 (0.6%)	1 (2.3%)	1 (1.3%)
Hypertension	5 (1.4%)	58 (16.0%)	1 (2.3%)	12 (15.0%)
LVSD	1 (0.3%)	8 (2.2%)	0 (0.0%)	0 (0.0%)
Neutropenia	14 (4.0%)	29 (8.0%)	2 (4.5%)	9 (11.3%)
Proteinuria	0 (0.0%)	11 (3.0%)	0 (0.0%)	6 (7.5%)
Sensory neuropathy	63 (18.1%)	90 (24.8%)	8 (18.2%)	9 (11.3%)
Venous thromboembolic event	15 (4.3%)	11 (3.0%)	2 (4.5%)	0 (0.0%)

Abr=nab-paclitaxel; GI=gastrointestinal; LVSD=left ventricular systolic dysfunction; Pac=paclitaxel.

Because the active moieties of nab-paclitaxel and paclitaxel are the same and the approval for nab-paclitaxel was based on efficacy comparable to that of paclitaxel, it can be extrapolated that the data from the nab-paclitaxel subgroup of RIBBON1 and from E2100 are supportive of each other. Therefore, one can conclude that Avastin in combination with either paclitaxel or nab-paclitaxel demonstrated a positive benefit–risk assessment when administered as first-line treatment for patients with HER2-negative MBC.

5.1.2 Docetaxel in Combination with Avastin

Data from two studies, AVADO and RIBBON1, support the benefit of Avastin in combination with docetaxel in HER2-negative MBC. The efficacy data for the docetaxel comparisons are outlined in Table 20. It should be noted that AVADO was specifically designed to evaluate the comparative efficacy of combining Avastin with docetaxel. The results for the evaluation of docetaxel+Avastin in RIBBON1 were derived from a subgroup of the efficacy cohort (181 of the 622 randomized patients).

Table 20
Efficacy Results for Docetaxel-Treated Patients in AVADO and RIBBON1

	AVADO		RIBBON1	
	Doc + Placebo (n = 241)	Doc + Avastin (n = 247)	Doc + Placebo (n = 58)	Doc + Avastin (n = 123)
PFS				
Patients with a PFS event	152 (63.1%)	134 (54.3%)	47 (81.0%)	78 (63.4%)
PFS (months)				
HR [a] (relative to Doc + placebo) (95% CI)	0.62 (0.48, 0.79)		0.87 (0.59; 1.27)	
Median	7.9	8.8	8.4	9.2
Objective response rate				
Patients with measurable disease	207	206	48	100
Objective response rate	92 (44.4%)	130 (63.1%)	20 (41.7%)	51 (51.0%)
Between-arm difference (95% CI)	18.7% (9.0%, 28.4%)		9.33% (−8.9%, 27.6%)	
Overall survival (updated) [b]				
Patients who died	108 (44.8 %)	116 (47.0 %)	21 (36.2%)	60 (48.8%)
Overall survival (months)				
HR [a] (relative to Doc + placebo) (95% CI)	1.00 (0.76, 1.32)		1.45 (0.88, 2.40)	
Median	31.9	30.2	NR	27.0

CI = confidence interval; Doc = docetaxel; HR = hazard ratio; NR = not reached; PFS = progression-free survival.

[a] Stratified analysis.

[b] The cutoff for the updated analysis of overall survival was 30 April 2009 for AVADO and 23 February 2009 for RIBBON1.

On the basis of historical data from many studies demonstrating median PFS of 6 months for docetaxel, the protocol for AVADO specified a target PFS hazard ratio of 0.70 (Lyseng-Williamson et al. 2005). The observed hazard ratio for PFS in AVADO was 0.62 (95% CI: 0.48, 0.79), a result that exceeded the protocol-specified target. Multiple sensitivity analyses of these data using different censoring parameters and in key clinical populations demonstrated a high degree of consistency with the primary analysis results.

Approximately 30% of the patients enrolled in the taxane/anthracycline cohort of RIBBON1 received docetaxel (58 patients received docetaxel + placebo and 123 patients received docetaxel + Avastin). The hazard ratio for PFS in this subgroup was 0.87 (95% CI: 0.59, 1.27), a result that is numerically higher than the overall results for RIBBON1 or AVADO. These results can be viewed as

supportive, given the wide confidence interval and the exploratory nature of this subgroup analysis.

The results from AVADO indicate that Avastin neither improved nor impaired overall survival. The overall survival results in the docetaxel-treated subgroup of RIBBON1 numerically favored the control arm, but full review and analysis did not identify a clinical rationale for this finding. The overall survival results for the docetaxel + Avastin arm of RIBBON1 were not reproduced by the much larger experience with docetaxel in AVADO, or supported by the overall survival results across all three breast cancer trials. This result may be a chance finding due to the multiple subgroups analyzed.

Table 21 shows the incidence of Grade ≥ 3 selected adverse events among docetaxel-treated patients. The incidence of neutropenia and febrile neutropenia, commonly associated with docetaxel administration, was higher in Avastin-containing arms of AVADO and RIBBON1 compared with the control arms. No imbalance in treatment-related deaths or study drug discontinuation due to neutropenia or febrile neutropenia was observed among docetaxel-treated patients.

Table 21
Incidence of Grade ≥3 Selected Adverse Events among Docetaxel-Treated Patients in AVADO and RIBBON1

Selected Adverse Event Category	AVADO			RIBBON1	
	Doc+Placebo (n=231)	Doc+Avastin7.5 (n=252)	Doc+Avastin (n=247)	Doc+Placebo (n=58)	Doc+Avastin (n=123)
Any Grade ≥3 selected adverse event	87 (37.7%)	108 (42.9%)	112 (45.3%)	11 (19.0%)	53 (43.1%)
Arterial thromboembolic event	1 (0.4%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	1 (0.8%)
Bleeding	2 (0.9%)	3 (1.2%)	3 (1.2%)	0 (0.0%)	6 (4.9%)
Febrile neutropenia	27 (11.7%)	38 (15.1%)	41 (16.6%)	2 (3.4%)	13 (10.6%)
GI perforation	2 (0.9%)	1 (0.4%)	1 (0.4%)	0 (0.0%)	3 (2.4%)
Hypertension	3 (1.3%)	2 (0.8%)	11 (4.5%)	1 (1.7%)	7 (5.7%)
LVSD	0 (0.0%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	4 (3.3%)
Neutropenia	45 (19.5%)	54 (21.4%)	52 (21.1%)	3 (5.2%)	10 (8.1%)
Proteinuria	0 (0.0%)	2 (0.8%)	5 (2.0%)	0 (0.0%)	2 (1.6%)
RPLS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Sensory neuropathy	10 (4.3%)	20 (7.9%)	19 (7.7%)	1 (1.7%)	8 (6.5%)
Venous thromboembolic event	8 (3.5%)	4 (1.6%)	3 (1.2%)	3 (5.2%)	4 (3.3%)

Doc=docetaxel; GI=gastrointestinal; LVSD=left ventricular systolic dysfunction; RPLS=reversible posterior leukoencephalopathy syndrome.

Note: Patients in the Doc+Avastin7.5 arm of AVADO received Avastin 7.5 mg/kg every 3 weeks; all other Avastin-treated patients received an Avastin dose of 15 mg/kg every 3 weeks until disease progression or toxicity.

In summary, the data from AVADO and RIBBON1 indicate that Avastin provided improved disease control when combined with docetaxel for the first-line treatment of patients with HER2-negative MBC. The safety profile of the combination was consistent with previous Avastin experience in other indications and with that described in the Avastin® U.S. Package Insert. No imbalance in treatment-related deaths was seen. Specific adverse events of clinical importance, such as neutropenia and febrile neutropenia, were observed at a higher frequency when Avastin was combined with taxane-based chemotherapy.

Together, these results support a favorable benefit–risk assessment for Avastin in combination with docetaxel as first-line treatment of patients with HER2-negative MBC.

5.2 ANTHRACYCLINES IN COMBINATION WITH AVASTIN

RIBBON1 was the only study that incorporated anthracyclines into the treatment regimen, and thus there is less information on this combination. Several anthracycline regimens typically used in clinical practice were allowed in RIBBON1:

- Doxorubicin + cyclophosphamide (AC)
- 5-Fluorouracil + doxorubicin + cyclophosphamide (FAC)
- Epirubicin + cyclophosphamide (EC)
- 5-Fluorouracil + epirubicin + cyclophosphamide (FEC)

The efficacy data for the subgroup of patients who received anthracycline-based chemotherapy in RIBBON1 are outlined in Table 22.

Table 22
Efficacy Results for Anthracycline-Treated Patients in RIBBON1

	Anth + Placebo (n = 103)	Anth + Avastin (n = 212)
PFS		
Patients with a PFS event	81 (78.6%)	124 (58.5%)
PFS (months)		
HR [a] (relative to Anth + placebo) (95% CI)	0.55 (0.40, 0.74)	
Median	7.9	9.2
Objective response rate		
Patients with measurable disease	92	184
Objective response rate	37 (40.2%)	96 (52.2%)
Between-arm difference (95% CI)	12% (−0.4%, 24.3%)	
Overall survival (updated) [b]		
Patients who died	44 (42.7%)	88 (41.5%)
Overall survival (months)		
HR [a] (relative to Anth + placebo) (95% CI)	0.97 (0.67, 1.41)	
Median	NR	28.7

Anth = anthracycline; CI = confidence interval; HR = hazard ratio; NR = not reached; PFS = progression-free survival.

[a] Stratified analysis.

[b] The cutoff for the updated analysis of overall survival was 23 February 2009 for RIBBON1.

Although the anthracycline-treated patients were a subgroup, the sample size of 315 patients had approximately 205 events observed. The upper limit of the 95% confidence interval for PFS was 0.74, indicating that these patients represent a sample of sufficient size to show a reliable and clinically meaningful improvement in PFS.

The sensitivity analyses performed to assess the reliability and robustness of the PFS results, including an analysis based on an independent radiology facility assessment, consistently indicated a treatment benefit for the combination of Avastin with anthracycline-based chemotherapy.

The adverse event profile for the combination of Avastin with anthracycline-based chemotherapy did not substantially differ from what is expected for these agents and was consistent with the profile reported in the Avastin® U.S. Package Insert. Table 23 shows the incidence of Grade ≥3 selected adverse events among anthracycline-treated patients in RIBBON1. Left ventricular systolic dysfunction (LVSD) was analyzed specifically for this combination because of the known cardiotoxicity associated with anthracyclines. Regular left ventricular ejection fraction (LVEF) assessments and symptom-directed physical examinations were performed to ensure the cardiac safety of study patients. The incidence of any grade LVSD was similar in the two treatment arms (6.2% in the anthracycline + Avastin arm vs. 6.2% in the anthracycline + placebo arm). Of the reports of LVSD, patients in the anthracycline + Avastin arm experienced more Grade ≥3 events (2.9%) than those in the control arm (0.0%); this incidence is consistent with that reported in the Avastin® U.S. Package insert.

Hypertension showed a ≥5% increase in incidence in the anthracycline + Avastin arm versus the anthracycline + placebo arm (10.0% vs. 0.0%, respectively); these were predominantly Grade 3 events.

Table 23
Incidence of Grade ≥3 Selected Adverse Events among Anthracycline-Treated Patients in RIBBON1

Selected Adverse Event Category	Anth + Placebo (n = 100)	Anth + Avastin (n = 210)
Any Grade ≥3 selected adverse event	11 (11.0%)	51 (24.3%)
Arterial thromboembolic event	0 (0.0%)	3 (1.4%)
Febrile neutropenia	5 (5.0%)	8 (3.8%)
Hypertension	0 (0.0%)	21 (10.0%)
LVSD	0 (0.0%)	6 (2.9%)
Neutropenia	4 (4.0%)	9 (4.3%)
Proteinuria	0 (0.0%)	4 (1.9%)
Sensory neuropathy	0 (0.0%)	1 (0.5%)
Venous thromboembolic event	2 (2.0%)	6 (2.9%)

Anth = anthracycline; LVSD = left ventricular systolic dysfunction.

In summary, Avastin in combination with anthracycline-based chemotherapy has a positive benefit–risk profile when administered as first-line treatment for patients with HER2-negative MBC.

5.3 CAPECITABINE IN COMBINATION WITH AVASTIN

The study design of RIBBON1 included an independently powered evaluation for capecitabine + Avastin compared with capecitabine + placebo. The randomized population comprised 409 patients in the capecitabine + Avastin arm and 206 patients in the capecitabine + placebo arm. As described in Section 4.1, the combination of Avastin with capecitabine led to a statistically significant and clinically meaningful improvement in disease control. The efficacy data for the capecitabine comparisons of RIBBON1 are outlined in Table 24.

Table 24
Efficacy Results for Capecitabine-Treated Patients in RIBBON1

	Cap + Placebo (n = 206)	Cap + Avastin (n = 409)
PFS		
Patients with a PFS event	162 (78.6%)	291 (71.1%)
PFS (months)		
HR [a] (relative to Cap + placebo) (95% CI)	0.69 (0.56, 0.84)	
Median	5.7	8.6
Objective response rate		
Patients with measurable disease	161	325
Objective response rate	38 (23.6%)	115 (35.4%)
Between-arm difference (95% CI)	11.8% (3.4%, 20.2%)	
Overall survival (updated) [b]		
Patients who died	99 (48.1%)	186 (45.5%)
Overall survival (months)		
HR [a] (relative to Cap + placebo) (95% CI)	0.88 (0.69, 1.13)	
Median	22.8	25.7

Cap = capecitabine; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival.

[a] Stratified analysis.

[b] The cutoff for the updated analysis of overall survival was 23 February 2009 for RIBBON1.

The sensitivity analyses performed to assess the reliability and robustness of the PFS results, including an analysis based on an independent radiology facility assessment, consistently indicated a treatment benefit associated with the combination of Avastin with capecitabine.

The Phase III trial AVF2119g also investigated Avastin in combination with capecitabine but did not meet its primary endpoint of PFS improvement. In contrast to RIBBON1, AVF2119g enrolled a heterogeneous population of patients whose MBC had progressed following one or two regimens for metastatic disease and who had previously received both an anthracycline and a taxane in any line of therapy, including adjuvant therapy. The majority of patients enrolled in AVF2119g received second-line treatment (44.3%; 205 of 462 patients) or third-line and later treatment (40.0%; 185 of 462 patients) on study and had progressed on both an anthracycline and a taxane at some point in their treatment course; 15.6% (72 of 462) of patients received first-line treatment on study after adjuvant treatment

with an anthracycline and a taxane and progression within 12 months of disease presentation. Additionally, approximately 23% of patients enrolled in AVF2119g had HER2-positive tumors. The AVF2119g first-line patient population was distinct from that enrolled in E2100, AVADO, and RIBBON1; fewer than 3% of the patients enrolled in AVF2119g would have met the inclusion criteria for the first-line studies. Because of these differences, it is difficult to compare the efficacy results from AVF2119g with those for the capecitabine-treated patients in RIBBON1. However, AVF2119g provides additional safety data for consideration.

Table 25 shows the incidence of Grade ≥3 selected adverse events reported in AVF2119g and among capecitabine-treated patients in RIBBON1. Data from AVF2119g indicate that the incidence of these adverse events was consistent with the RIBBON1 findings.

Table 25
Incidence of Grade ≥3 Selected Adverse Events among Capecitabine-Treated Patients in RIBBON1 and AVF2119g

	RIBBON1		AVF2119g	
Selected Adverse Event Category	Cap+Placebo (n=201)	Cap+Avastin (n=404)	Cap (n=215)	Cap+Avastin (n=229)
Any Grade ≥3 selected adverse event	17 (8.5%)	87 (21.5%)	20 (9.3%)	70 (30.6%)
Arterial thromboembolic event	2 (1.0%)	8 (2.0%)	1 (0.5%)	0 (0.0%)
Bleeding	1 (0.5%)	1 (0.2%)	1 (0.5%)	1 (0.4%)
Febrile neutropenia	0 (0.0%)	0 (0.0%)	2 (0.9%)	0 (0.0%)
Hypertension	2 (1.0%)	40 (9.9%)	1 (0.5%)	46 (20.1%)
LVSD	1 (0.5%)	4 (1.0%)	2 (0.9%)	8 (3.5%)
Neutropenia	2 (1.0%)	5 (1.2%)	5 (2.3%)	6 (2.6%)
Proteinuria	0 (0.0%)	9 (2.2%)	0 (0.0%)	2 (0.9%)
Sensory neuropathy	1 (0.5%)	12 (3.0%)	2 (0.9%)	1 (0.4%)
Venous thromboembolic event	7 (3.5%)	19 (4.7%)	7 (3.3%)	14 (6.1%)

Cap=capecitabine; LVSD=left ventricular systolic dysfunction.

Adverse events commonly associated with capecitabine were assessed in AVF2119g. The incidence of these events (of any grade) was not substantially increased with the combination of Avastin with capecitabine compared with capecitabine alone. For example, in patients receiving capecitabine+Avastin compared with capecitabine alone, palmar-plantar erthrodysaesthesia was

reported in 84% versus 75% of patients and diarrhea was reported in 58% versus 53% of patients, respectively.

In summary, the combination of Avastin with capecitabine did not lead to clinically significant increases in toxicity, including events commonly seen with capecitabine. Overall, the safety profile observed for Avastin in combination with capecitabine was consistent with the well-characterized profile described for other indications and in the Avastin® U.S. Package Insert. Avastin in combination with capecitabine has a positive benefit–risk profile when administered as first-line treatment of patients with HER2-negative MBC.

5.4 SUMMARY AND DISCUSSION OF DATA TO SUPPORT THE PROPOSED AVASTIN INDICATION

Three Phase III, controlled clinical trials of Avastin in combination with multiple classes of chemotherapeutic agents were conducted in a heterogeneous, previously untreated HER2-negative MBC population. The results from the first trial, E2100, initially established that the combination of Avastin with first-line paclitaxel improved PFS, leading to the accelerated approval of Avastin in HER2-negative MBC. Two additional well-conducted studies, comprising three independent efficacy comparisons, have reliably reproduced those results. All studies demonstrated similar findings, with increased PFS (see Table 26) and objective response rates in the overall study population, as well as in key patient subgroups.

Table 26
Primary Analysis of Progression-Free Survival

					RIBBON1			
	E2100		AVADO		T/Anth Comparison		Cap Comparison	
	Pac (n=354)	Pac+ Avastin (n=368)	Doc+ Placebo (n=241)	Doc+ Avastin (n=247)	T/Anth+ Placebo (n=207)	T/Anth+ Avastin (n=415)	Cap+ Placebo (n=206)	Cap+ Avastin (n=409)
HR	0.48		0.62		0.64		0.69	
(95% CI)	(0.39, 0.61)		(0.48, 0.79)		(0.52, 0.80)		(0.56, 0.84)	
p-value	<0.0001		0.0003		<0.0001		0.0002	

Cap=capecitabine; CI=confidence interval; Doc=docetaxel; HR=hazard ratio; Pac=paclitaxel; T/Anth=taxane/anthracycline.

The combination of Avastin with standard chemotherapy regimens resulted in a consistent safety profile, no impairment of overall survival, and no incremental worsening of HRQOL. Taken together, these data present evidence of consistent clinical benefit for the combination of Avastin with chemotherapy, independent of the underlying chemotherapy class, and serve as the basis for the indication being requested: Avastin, in combination with taxane-based, anthracycline-based, or capecitabine chemotherapy, is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

6. OVERALL CONCLUSIONS

All three studies of Avastin in combination with chemotherapy in patients with newly diagnosed, previously untreated MBC demonstrated consistent efficacy and safety findings:

- The combination of Avastin with chemotherapy led to statistically significant and clinically meaningful improvements in PFS, with hazard ratios ranging between 0.48 and 0.69.
- Consistent improvement in PFS was seen across key patient subgroups, including those with poor prognostic disease characteristics.
- Increases in objective response rate were seen when Avastin was combined with various chemotherapies, regardless of the control objective response rate.
- Overall survival was not impaired, as shown in the individual studies, with long median follow-up (23 to 35 months).
- Minimal impact on health-related quality of life was seen when Avastin was combined with taxane therapy.
- The adverse event profile was predictable and consistent with the Avastin experience in other tumor indications.
- No substantial exacerbation of the known toxicities of the chemotherapy partner or limitation of chemotherapy delivery was observed with the addition of Avastin.

The data from these three studies in the first-line MBC setting provide objective, consistent evidence of the benefit of treatment with Avastin in combination with standard chemotherapy regimens. The benefit of combining Avastin with standard first-line chemotherapy outweighed the manageable incremental increase in toxicity incurred. The choice of chemotherapy to be used with Avastin will be dictated by the needs of the individual patient, considering both the efficacy and safety of each combination therapy. The proposed Avastin dosing schedule of every 2 or 3 weeks allows clinicians flexibility in combining Avastin with standard cytotoxic therapy regimens for the first-line treatment of patients with HER2-negative MBC.

In conclusion, we now have substantial evidence that meets the criteria set forth by the FDA to convert the accelerated approval of Avastin for the treatment of patients who have not received chemotherapy for their HER2-negative MBC to full approval. The data presented in this briefing book, based on more than

2400 patients, reliably and consistently demonstrate that treatment with Avastin in combination with chemotherapy provided clinical benefit, as measured by PFS, in women with newly diagnosed, previously untreated MBC. These improvements in PFS were seen in major chemotherapy classes and across clinically important patient subpopulations. The safety data presented here confirm Avastin's favorable benefit–risk profile. Results from RIBBON1 and AVADO indicate that Avastin did not impact a patient's health-related quality of life more than chemotherapy alone. Taken together, these data consistently demonstrate that treatment with Avastin in combination with chemotherapy provides clinically meaningful benefit to patients with newly diagnosed, previously untreated HER2-negative MBC.

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8. APPENDICES

Appendix A: E2100 Approval Letter

Appendix B: Avastin® U.S. Package Insert

Appendix C: Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

Appendix D: Regulatory History of Clinical Development Program of Avastin in Metastatic Breast Cancer

Appendix E: Summary of Results for the 7.5 mg/kg Arm of AVADO

Appendix F: Statistical Methodology

APPENDIX A
E2100 Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125085/91

FEB 22 2008

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

Dear Dr. Rich:

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

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

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

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

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

1. To submit an efficacy supplement containing the final study reports (including summary analyses and primary datasets) and revised labeling based on the results from both of the following studies:

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

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

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

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

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

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

2. To submit a clinical study report, including summary analyses and primary datasets, for study AVF3693g, "A Phase 3, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Treated Metastatic Breast Cancer." The protocol was submitted to IND 7023 on January 9, 2007. Patient accrual will completed by June 30, 2009, and the study completed by March 31, 2010. The clinical study report will be submitted by January 31, 2011.

3. To submit a clinical study report, including summary analyses and datasets, for study BO20231, "A Randomized, Open-Label, 2-Arm, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Trastuzumab/Docetaxel Compared with Trastuzumab/Docetaxel Alone as First Line Treatment for Patients with HER2 Positive Locally Recurrent or Metastatic Cancer." The protocol was submitted to IND 7023 on February 20, 2007. Patient accrual will completed by July 31, 2011, and the study completed by April 30, 2012. The clinical study report will be submitted by April 1, 2013.

4. To submit a clinical study report, including summary analyses and datasets, for study CALGB 40503, "A Endocrine Therapy in Combination with Anti-VEGF Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Endocrine Therapy Alone or Endocrine Therapy plus Bevacizumab for Women with Hormone-Receptor Positive Advanced Breast Cancer.". The protocol was submitted to IND 7023 on January 19, 2007. Patient accrual will completed by February 29, 2012, and the study completed by September 30, 2012. The clinical study report will be submitted by December 31, 2013.

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

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

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

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

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

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 125085/91." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

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

As required by 21 CFR 601.45, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement with a cover letter requesting advisory comment. Send two copies of the promotional materials to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-

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

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

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

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

Sincerely,

Richard Pazdur MD

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Revised Labeling

APPENDIX B
Avastin® U.S. Package Insert

1.14.2.3 Final Labeling Text

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AVASTIN safely and effectively. See full prescribing information for AVASTIN.

AVASTIN® (bevacizumab)
Solution for intravenous infusion
Initial U.S. Approval: 2004

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE
See full prescribing information for complete boxed warning.
- **Gastrointestinal Perforation: Occurs in up to 2.4% of Avastin-treated patients. Discontinue Avastin for gastrointestinal perforation. (5.1)**
- **Surgery and Wound Healing Complications: Discontinue in patients with wound dehiscence. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. (5.2)**
- **Hemorrhage: Severe or fatal hemorrhage, hemoptysis, gastrointestinal bleeding, CNS hemorrhage, and vaginal bleeding are increased in Avastin- treated patients. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. (5.3)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Glioblastoma (1.4)	5/2009
Indications and Usage, Renal Cell Carcinoma (1.5)	7/2009
Dosage and Administration, Glioblastoma (2.2)	5/2009
Dosage and Administration, Renal Cell Carcinoma (2.2)	7/2009
Warnings and Precautions, Hemorrhage (5.3)	5/2009
Warnings and Precautions, Proteinuria (5.8)	7/2009

----------INDICATIONS AND USAGE----------

Avastin is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment. (1.1)
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)
- Metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer. (1.3)
  -Effectiveness based on improvement in progression-free survival. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
  -Not indicated for disease progression following anthracycline and taxane chemotherapy administered for metastatic disease.
- Glioblastoma, as a single agent for patients with progressive disease following prior therapy. (1.4)
  -Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
- Metastatic renal cell carcinoma with interferon alfa (1.5)

----------DOSAGE AND ADMINISTRATION----------

- Do not administer as an IV push or bolus. (2.1)
- Do not initiate Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)

Metastatic colorectal cancer (2.2)
- 5 mg/kg IV every 2 weeks with bolus-IFL
- 10 mg/kg IV every 2 weeks with FOLFOX4

Non–squamous non–small cell lung cancer (2.2)
- 15 mg/kg IV every 3 weeks with carboplatin/paclitaxel

Metastatic breast cancer (2.2)
- 10 mg/kg IV every 2 weeks with paclitaxel

Glioblastoma (2.2)
- 10 mg/kg IV every 2 weeks

Metastatic renal cell carcinoma (mRCC) (2.2)
- 10 mg/kg IV every 2 weeks with interferon alfa

----------DOSAGE FORMS AND STRENGTHS----------

- 100 mg/4 mL, single use vial (3)
- 400 mg/16 mL, single use vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Non-Gastrointestinal Fistula Formation: Discontinue Avastin if fistula formation occurs. (5.4)
- Arterial Thromboembolic Events (e.g., myocardial infarction, cerebral infarction): Discontinue Avastin for severe ATE. (5.5)
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend Avastin if not medically controlled. Discontinue Avastin for hypertensive crisis or hypertensive encephalopathy. (5.6)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue Avastin. (5.7)
- Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Temporarily suspend Avastin for moderate proteinuria. (5.8)
- Infusion Reactions: Stop for severe infusion reactions. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions incidence (>10% and at least twice the control arm rate) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: July 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

Gastrointestinal Perforations

The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. *[See Dosage and Administration (2.4), Warnings and Precautions (5.1).]*

Surgery and Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. *[See Dosage and Administration (2.4), Warnings and Precautions (5.2), and Adverse Reactions (6.1).]*

Hemorrhage

Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. *[See Dosage and Administration (2.4), Warnings and Precautions (5.3), and Adverse Reactions (6.1).]*

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

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

1.2 Non-Squamous Non–Small Cell Lung Cancer (NSCLC)

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

1.3 Metastatic Breast Cancer (MBC)

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

The effectiveness of Avastin in MBC is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. *[See Clinical Studies (14.3).]*

Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

1.4 Glioblastoma

Avastin is indicated for the treatment of glioblastoma with progressive disease following prior therapy as a single agent.

The effectiveness of Avastin in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. *[See Clinical Studies (14.4).]*

1.5 Metastatic Renal Cell Carcinoma (mRCC)

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion.

- Do not initiate Avastin until at least 28 days following major surgery. Administer Avastin after the surgical incision has fully healed.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

2.2 Recommended Doses and Schedules

Patients should continue treatment until disease progression or unacceptable toxicity.

Metastatic Colorectal Cancer (mCRC)

The recommended doses are 5 mg/kg or 10 mg/kg every 2 weeks when used in combination with intravenous 5-FU-based chemotherapy.

- Administer 5 mg/kg when used in combination with bolus-IFL.
- Administer 10 mg/kg when used in combination with FOLFOX4.

Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

The recommended dose is 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel.

Metastatic Breast Cancer (MBC)

The recommended dose is 10 mg/kg every 2 weeks in combination with paclitaxel.

Glioblastoma

The recommended dose is 10 mg/kg every 2 weeks.

Metastatic Renal Cell Carcinoma (mRCC)

The recommended dose is 10 mg/kg every 2 weeks in combination with interferon alfa.

2.3 Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Withdraw necessary amount of Avastin 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.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

2.4 Dose Modifications

There are no recommended dose reductions.

Discontinue Avastin for:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ *[See Boxed Warning, Warnings and Precautions (5.1, 5.4).]*
- Wound dehiscence and wound healing complications requiring medical intervention *[See Warnings and Precautions (5.2).]*
- Serious hemorrhage (i.e., requiring medical intervention*) [See Boxed Warning, Warnings and Precautions (5.3).]*
- Severe arterial thromboembolic events *[See Warnings and Precautions (5.5).]*
- Hypertensive crisis or hypertensive encephalopathy *[See Warnings and Precautions (5.6).]*

- Reversible posterior leukoencephalopathy syndrome (RPLS) *[See Warnings and Precautions (5.7).]*
- Nephrotic syndrome *[See Warnings and Precautions (5.8).]*

Temporarily suspend Avastin for:
- At least 4 weeks prior to elective surgery *[See Warnings and Precautions (5.2).]*
- Severe hypertension not controlled with medical management *[See Warnings and Precautions (5.6).]*
- Moderate to severe proteinuria pending further evaluation *[See Warnings and Precautions (5.8).]*
- Severe infusion reactions *[See Warnings and Precautions (5.9).]*

3 DOSAGE FORMS AND STRENGTHS

100 mg per 4 mL single-use vial
400 mg per 16 mL single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies. *[See Adverse Reactions (6.1).]*

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of Avastin.

Discontinue Avastin in patients with gastrointestinal perforation. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.2 Surgery and Wound Healing Complications

Avastin impairs wound healing in animal models. *[See Nonclinical Toxicology (13.2).]* In clinical trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of Avastin treatment was 15% and in patients who did not receive Avastin, was 4%. *[See Adverse Reactions (6.1).]*

Avastin should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue Avastin in patients with wound healing complications requiring medical intervention.

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. Suspend Avastin for at least 28 days prior to elective surgery. Do not administer Avastin until the wound is fully healed. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3

hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. *[See Adverse Reactions (6.1).]*

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving Avastin and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3–4 hemorrhage.

Do not administer Avastin to patients with recent history of hemoptysis of ≥1/2 teaspoon of red blood. Discontinue Avastin in patients with hemorrhage. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.4 Non-Gastrointestinal Fistula Formation

Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in Avastin-treated patients compared to controls. The incidence of non-gastrointestinal perforation was ≤0.3% in clinical studies. Most events occurred within the first 6 months of Avastin therapy.

Discontinue Avastin in patients with fistula formation involving an internal organ. *[See Dosage and Administration (2.4).]*

5.5 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.4% compared to 0.7% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years. *[See Use in Specific Populations (8.5).]*

The safety of resumption of Avastin therapy after resolution of an ATE has not been studied. Discontinue Avastin in patients who experience a severe ATE. *[See Dosage and Administration (2.4).]*

5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuation of Avastin.

Temporarily suspend Avastin in patients with severe hypertension that is not controlled with medical management. Discontinue Avastin in patients with hypertensive crisis or hypertensive encephalopathy. *[See Dosage and Administration (2.4).]*

5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been reported with an incidence of <0.1% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of Avastin. 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. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS.

Discontinue Avastin in patients developing RPLS. 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. *[See Dosage and Administration (2.4).]*

5.8 Proteinuria

The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to controls. Nephrotic syndrome occurred in < 1% of patients receiving Avastin in clinical trials, in some instances with fatal outcome. *[See Adverse Reactions (6.1).]* In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57). *[See Use in Specific Populations (8.5).]* The safety of continued Avastin treatment in patients with moderate to severe proteinuria has not been evaluated. *[See Dosage and Administration (2.4).]*

5.9 Infusion Reactions

Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of Avastin were uncommon (< 3%) and severe reactions occurred in 0.2% of patients.

Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy. *[See Dosage and Administration (2.4).]*

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Gastrointestinal Perforations *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.1).]*
- Surgery and Wound Healing Complications *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).]*
- Hemorrhage *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).]*
- Non-Gastrointestinal Fistula Formation *[See Dosage and Administration (2.4), Warnings and Precautions (5.4).]*
- Arterial Thromboembolic Events *[See Dosage and Administration (2.4), Warnings and Precautions (5.5).]*
- Hypertensive Crisis *[See Dosage and Administration (2.4), Warnings and Precautions (5.6).]*
- Reversible Posterior Leukoencephalopathy Syndrome *[See Dosage and Administration (2.4), Warnings and Precautions (5.7).]*
- Proteinuria *[See Dosage and Administration (2.4), Warnings and Precautions (5.8).]*

The most common adverse reactions observed in Avastin patients at a rate > 10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

Across all studies, Avastin was discontinued in 8.4 to 21% of patients because of adverse reactions.

6.1 Clinical Trial Experience

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 data below reflect exposure to Avastin in 2661 patients with mCRC, non-squamous NSCLC, MBC, glioblastoma, or mRCC in controlled (Studies 1, 2, 4, 5, 6 and 9) or uncontrolled, single arm (Study 7) trials treated at the recommended dose and schedule for a median of 8 to 16 doses of Avastin. *[See Clinical Studies (14).]* The population was aged 21-88 years (median 59), 46.0% male and 84.1% white. The population included 1089 first- and second-line mCRC patients who received a median of 11 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 592 MBC patients who had not received chemotherapy for metastatic disease received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin.

Surgery and 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 Study 7, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).]*

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. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).]*

Venous Thromboembolic Events

The incidence of 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. The risk of developing a second subsequent thromboembolic event in mCRC patients receiving Avastin and chemotherapy was 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 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 Grade 3–4 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).

Neutropenia and Infection

The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving paclitaxel/carboplatin (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 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%)].

In Study 7, one fatal event of neutropenic infection occurred in a patient with previously treated glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 9. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 9, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 9). *[See Warnings and Precautions (5.8).]*

Congestive Heart Failure

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin compared to 0.6% in the control arm across indications. In patients with MBC, the incidence of Grade 3-4 congestive heart failure (CHF) was increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

Metastatic Colorectal Cancer (mCRC)

The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus Avastin with chemotherapy plus placebo. Avastin was administered at 5 mg/kg every 2 weeks.

All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Severe and life-threatening (Grade 3–4) 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 1.

Table 1
NCI-CTC Grade 3–4 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	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
Leukopenia	31%	37%
Neutropenia[a]	14%	21%

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

Grade 1–4 adverse events which occurred at a higher incidence (≥ 5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2. Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

Table 2
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	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%

Table 2 (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)
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

Only Grade 3-5 non-hematologic and Grade 4–5 hematologic adverse events related to treatment were collected in Study 2. The most frequent adverse events (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events) occurring at a higher incidence (≥ 2%) in 287 patients receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 2.

Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 4. Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events (occurring at a higher incidence (≥2%) in 427 patients receiving PC plus Avastin compared with 441 patients receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Metastatic Breast Cancer (MBC)

Only Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events were collected in Study 5. Grade 3–4 adverse events occurring at a higher incidence (≥2%) in 363 patients receiving paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%), bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3% vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/desquamation (3% vs. 0.3%) and proteinuria (3% vs. 0%).

Sensory neuropathy, hypertension, and fatigue were reported at a ≥ 5% higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.

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

Avastin is not approved for use in combination with capecitabine or for use in second or third line treatment of MBC. The data below are presented to provide information on the overall safety profile of Avastin in women with breast cancer since Study 6 is the only randomized, controlled study in which all adverse events were collected for all patients. All patients in Study 6 received prior anthracycline and taxane therapy in the adjuvant setting or for metastatic disease. Grade 1–4 events which occurred at a higher incidence (≥5%) in patients receiving capecitabine plus Avastin compared to the capecitabine alone arm are presented in Table 3.

Table 3
NCI-CTC Grade 1–4 Adverse Events in Study 6 (Occurring at Higher Incidence [≥5%] in Capecitabine + Avastin vs. Capecitabine Alone)

	Capecitabine (n=215)	Capecitabine + Avastin (n=229)
Body as a Whole		
Asthenia	47%	57%
Headache	13%	33%
Pain	25%	31%
Cardiovascular		
Hypertension	2%	24%
Digestive		
Stomatitis	19%	25%
Metabolic/Nutrition		
Weight loss	4%	9%
Musculoskeletal		
Myalgia	8%	14%
Respiratory		
Dyspnea	18%	27%
Epistaxis	1%	16%
Skin/Appendages		
Exfoliative dermatitis	75%	84%
Urogenital		
Albuminuria	7%	22%

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 7 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

In patients receiving Avastin alone (N=84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving Avastin alone or Avastin plus irinotecan (N=163), the incidence of Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%).

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 9. Grade 3–5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving interferon alfa (IFN-α) plus Avastin compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

Grade 1–5 adverse events occurring at a higher incidence (≥5%) in patients receiving IFN-α plus Avastin compared to the IFN-α plus placebo arm are presented in Table 4.

Table 4
NCI-CTC Grades 1–5 Adverse Events in Study 9 (Occuring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

System Organ Class/Preferred term*	IFN-α +Placebo (n=304)	IFN-α + Avastin (n=337)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
Hypertension	9%	28%

*Adverse events were encoded using MedDRA, Version 10.1.

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus Avastin arm compared to IFN-α alone and not represented in Table 4: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 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.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis
Cardiovascular: Pulmonary hypertension, RPLS
Digestive: Intestinal necrosis, mesenteric venous occlusion, anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation, dysphonia

7 DRUG INTERACTIONS

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In a randomized study in 99 patients with NSCLC, 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.

In Study 9, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There *are no studies of bevacizumab in pregnant women. Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab resulted in teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions.* [See Nonclinical Toxicology (13.3).]

Human IgG is known to cross the placental barrier; therefore, bevacizumab may be transmitted from *the* mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Because of the observed teratogenic effects of known inhibitors of angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the half-life of the bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the mother. *[See Clinical Pharmacology (12.3).]*

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established.

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥ 2%) in patients aged ≥65 years as compared to younger patients 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 2, patients aged≥ 65 years 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 4, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. *[See Warnings and Precautions (5.8).]*

In Study 5, there were insufficient numbers of patients ≥ 65 years old to determine whether the overall adverse events profile was different in the elderly as compared with 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 aged≥65 years and 1127 patients<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 aged≥65 years (8.5% vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). *[See Warnings and Precautions (5.5).]*

10 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.

11 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. Avastin has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous 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.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.3 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, gender, and 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 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies of bevacizumab have been conducted.

Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. 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; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

13.2 Animal Toxicology and/or Pharmacology

In cynomolgus monkeys, when bevacizumab was administered at doses of 0.4 to 20 times the weekly human exposure, anatomical pathology revealed several adverse effects on general growth and skeletal development, fertility and wound healing capacity. Severe physeal dysplasia was consistently reported in juvenile monkeys with open growth plates receiving 0.4 to 20 times the human dose. The physeal dysplasia was characterized by a linear cessation of growth line and chondrocyte hyperplasia which did not completely resolve after the 4 to 12 weeks recovery period without drug exposure.

Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure.

13.3 Reproductive and Developmental Toxicology

Pregnant rabbits dosed with 1 to 12 times the human dose of bevacizumab every three days during the period of organogenesis (gestation day 6-18) exhibited teratogenic effects, decreases in maternal and fetal body weights, and increased number of fetal resorptions. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; meningocele; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges. There are no data available regarding the level of bevacizumab exposure in the offspring.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer (mCRC)

Study 1

In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL (irinotecan 125 mg/m^2, 5-FU 500 mg/m^2, and leucovorin (LV) 20 mg/m^2 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. The main outcome measure was overall survival (OS).

Of the 813 patients randomized to Arms 1 and 2, the median age was 60, 40% were female, 79% were Caucasian, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28% received prior adjuvant chemotherapy. In 56% of the patients, the dominant site of disease was extra-abdominal, while the liver was the dominant site in 38% of patients.

The addition of Avastin resulted in an improvement in survival across subgroups defined by age (< 65 yrs, ≥ 65 yrs) and gender. Results are presented in Table 5 and Figure 1.

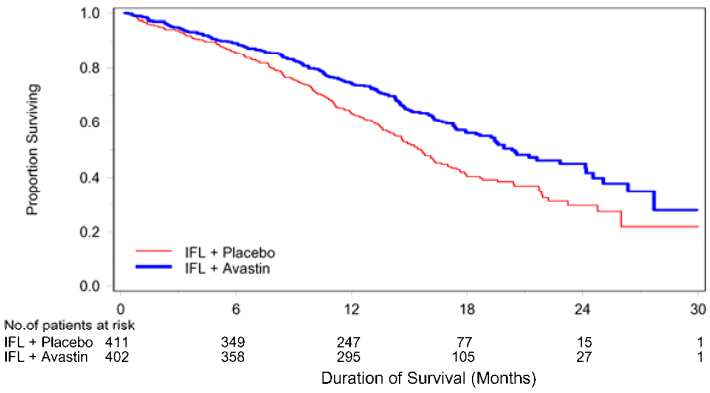
Table 5
Study 1 Efficacy Results

	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 log rank test.

[b] $p<0.01$ by χ^2 test.

Figure 1
Duration of Survival in Study 1



Among the 110 patients enrolled in Arm 3, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, objective response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study 2

Study 2 was a randomized, open-label, active-controlled trial in patients who were previously treated with irinotecan +/- 5-FU for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and LV 200 mg/m^2 concurrently, then 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; Day 2: LV 200 mg/m^2, then 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; repeated every

2 weeks), FOLFOX4 plus Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or Avastin monotherapy(10 mg/kg every 2 weeks). The main outcome measure was OS.

The Avastin monotherapy arm was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee based on evidence of decreased survival compared to FOLFOX4 alone.

Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female, 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as adjuvant therapy.

The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to FOLFOX4 alone (median OS 13.0 months vs. 10.8 months; hazard ratio 0.75 [95% CI 0.63, 0.89], $p=0.001$ stratified log rank test) with clinical benefit seen in subgroups defined by age (<65 yrs, ≥ 65 yrs) and gender. PFS and ORR based on investigator assessment were higher in the Avastin plus FOLFOX4 arm.

Study 3

The activity of Avastin in combination with bolus or infusional 5-FU/LV was evaluated in a single arm study enrolling 339 patients with mCRC with disease progression following both irinotecan- and oxaliplatin-containing chemotherapy regimens. Seventy-three percent of patients received concurrent bolus 5-FU/LV. One objective partial response was verified in the first 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

14.2 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)

Study 4

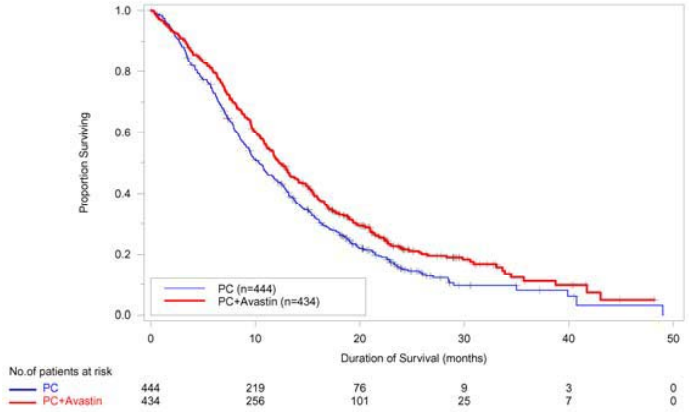
The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study.

Chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel 200 mg/m^2 and carboplatin AUC=6.0, by IV on day 1 (PC) or PC in combination with Avastin 15 mg/kg by IV 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. Patients with predominant squamous histology (mixed cell type tumors only), central nervous system (CNS) metastasis, gross hemoptysis (≥1/2 tsp of red blood), unstable angina, or receiving therapeutic anticoagulation were excluded. The main outcome measure was duration of survival.

Of the 878 patients randomized, 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 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

The results are presented in Figure 2. OS was statistically significantly higher among patients receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs. 10.3 months [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 PFS with Avastin in combination with PC compared to PC alone.

Figure 2
Duration of Survival in Study 4



In an exploratory analyses across patient subgroups, the impact of Avastin on OS 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)].

14.3 Metastatic Breast Cancer (MBC)

Study 5

The efficacy and safety of Avastin as first-line treatment of patients with MBC was studied in a single, open-label, randomized, multicenter study. Patients who had not received chemotherapy for locally recurrent or MBC were randomized (1:1) to receive paclitaxel (90 mg/m^2 IV once weekly for 3 out of 4 weeks) alone or in combination with Avastin (10 mg/kg IV infusion every 2 weeks). Patients were treated until disease progression or unacceptable toxicity. In situations where paclitaxel was discontinued or held, treatment with Avastin alone could be continued until disease progression. Patients with breast cancer overexpressing HER2 were not eligible unless they had received prior therapy with trastuzumab.

Prior hormonal therapy for the treatment of metastatic disease was allowed, as was prior adjuvant chemotherapy or hormonal therapy. Adjuvant taxane therapy, if received, must have been completed 12 or more months prior to study entry. Patients with central nervous system metastasis were excluded. The main outcome measure of the study was PFS as assessed by independent radiographic review. Secondary outcome measures were OS and ORR.

Of the 722 patients randomized, the median age was 55 years, 76% were white, 55% were postmenopausal, and 64% were ER and/or PR positive. Patient characteristics were similar across treatment arms. Thirty-six percent had received prior hormonal therapy for advanced disease, and 66% had received adjuvant chemotherapy, including 20% with prior taxane use and 50% with prior anthracycline use. Efficacy results are summarized in Table 6.

Table 6
Avastin Efficacy Results from Study 5

Efficacy Parameter	Avastin + Paclitaxel (n=368)	Paclitaxel Alone (n=354)	p-value	HR (95% CI)
Progression-free Survival	11.3	5.8		0.48
[median, months (95% CI)]	(10.5, 13.3)	(5.4, 8.2)	<0.0001	(0.39, 0.61)
Overall Survival	26.5	24.8		0.87
[median, months (95% CI)]	(23.7, 29.2)	(21.4, 27.4)	0.14	(0.72, 1.05)
Partial Response Rate[1] (PR)	48.9%[2]	22.2%	<0.001	—

[1] Includes only patients with measurable disease.
[2] The difference in partial response rates is 26.7% with a 95% CI (18.4%, 35.0%).

The addition of Avastin to paclitaxel resulted in an improvement in PFS with no significant improvement in OS. Partial response rates in patients with measurable disease were higher with Avastin plus paclitaxel. No complete responses were observed.

Thirty-four percent of the patients had incomplete follow-up for disease progression; therefore an exploratory analysis using similar imputation between arms was performed, which yielded a hazard ratio of 0.57.

Study 6

The efficacy and safety of Avastin as second- and third-line treatment of patients with MBC was studied in a single open-label randomized study. Patients who had received prior anthracycline and taxane therapy in the adjuvant setting or for their MBC were randomized (1:1) to receive capecitabine alone or in combination with Avastin. Of the 462 enrolled patients, the median age was 51 years, 81% were white, and 50% were ER positive. Patient characteristics were similar across the treatment arms.

The study failed to demonstrate a statistically significant effect on PFS or OS. The median PFS was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm (log-rank p-value = 0.86, hazard ratio 0.98). The median OS was 14.5 months in the capecitabine arm and 15.1 months in the capecitabine plus Avastin arm (hazard ratio of 1.08).

14.4 Glioblastoma

Study 7

The efficacy and safety of Avastin was evaluated in Study 7, an open-label, multicenter, randomized, non-comparative study of patients with previously treated glioblastoma. Patients received Avastin (10 mg/kg IV) alone or Avastin plus irinotecan every 2 weeks until disease progression or until unacceptable toxicity. All patients received prior radiotherapy (completed at least 8 weeks prior to receiving Avastin) and temozolomide. Patients with active brain hemorrhage were excluded.

Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for 55%.

The efficacy of Avastin was demonstrated using response assessment based on both WHO radiographic criteria and by stable or decreasing corticosteroid use, which occurred in 25.9% (95% CI 17.0%, 36.1%) of the patients. Median duration of response was 4.2 months (95% CI 3.0, 5.7). Radiologic assessment was based on MRI imaging (using T1 and T2/FLAIR). MRI does not necessarily distinguish between tumor, edema, and radiation necrosis.

Study 8

Study 8, was a single-arm, single institution trial with 56 patients with glioblastoma. All patients had documented disease progression after receiving temozolomide and radiation therapy. Patients received Avastin 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

The median age was 54, 54% were male, 98% Caucasian, and 68% had a Karnofsky Performance Status of 90–100.

The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%, 31.3%) using the same response criteria as in Study 7. Median duration of response was 3.9 months (95% CI 2.4, 17.4).

14.5 Metastatic Renal Cell Carcinoma (mRCC)

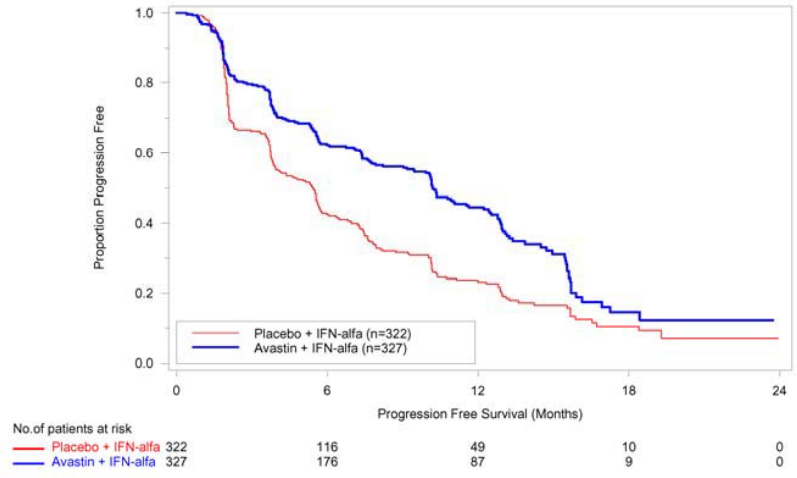
Study 9

Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind, international study comparing Avastin plus interferon alfa 2a (IFN- α2a) versus placebo plus IFN-α2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks; n=322) in combination with IFN-α2a (9 MIU subcutaneously three times weekly, for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3-5), and 7% missing.

The results are presented in Figure 3. PFS was statistically significantly prolonged among patients receiving Avastin plus IFN-α2a compared to those receiving IFN-α2a alone; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value < 0.0001, stratified log-rank test]. Among the 595 patients with measureable disease, ORR was also significantly higher (30% vs. 12%, p < 0.0001, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN-α2a arm and 21 months in the IFN-α2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

Figure 3
Progression-Free Survival in Study 9



16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2–8°C (36–46°F). Avastin vials should be protected from light. **Do not freeze or shake.**

Diluted Avastin solutions may be stored at 2–8°C (36–46°F) for up to 8 hours. Store in the original carton until time of use. No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated.
- To immediately contact their health care provider for unusual bleeding, high fever, rigors, sudden onset of worsening neurological function, or persistent or severe abdominal pain, severe constipation, or vomiting.
- Of increased risk of wound healing complications during and following Avastin.
- Of increased risk of an arterial thromboembolic event.
- Of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following last dose of Avastin.

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

7455316
LV0017
4835706
Initial U.S.Approval: February 2004
Code Revision Date: July 2009
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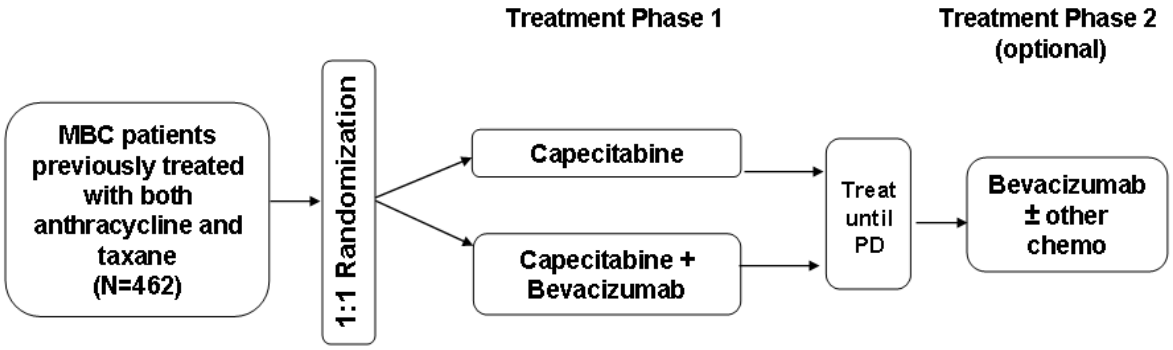
APPENDIX C
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

As discussed in Section 3.3 and presented in Figure 2 of this document, Genentech has a comprehensive development program in breast cancer. Multiple randomized, Phase III studies of Avastin (bevacizumab) in combination with chemotherapy, hormonal therapy, or trastuzumab for the treatment of patients with early-stage or MBC are completed or are ongoing. The purpose of this appendix is to provide a high-level overview of the study designs and key features of the completed and ongoing trials to support expanded labeling for Avastin in breast cancer. In this appendix, Avastin is referred to as bevacizumab. Study schemas in this appendix use the term bevacizumab for Avastin.

Metastatic Breast Cancer

1) Study AVF2119g

AVF2119g Study Design



PD = progressive disease.

- Multicenter, randomized, open-label, controlled, Phase III trial that investigated the combination of capecitabine + Avastin compared with capecitabine alone.
- Conducted in the United States by Genentech.
- Patient population: advanced MBC; eligible patients had MBC that had progressed following one or two regimens for metastatic disease, or following adjuvant therapy with a regimen containing both an anthracycline and a taxane and at least one, but no more than two, prior chemotherapy regimens for metastatic disease.
- Randomization: 1:1 to capecitabine + Avastin or capecitabine alone.
- Stratification factors: ECOG performance status (0, ≥1) and previous chemotherapy regimens (0, ≥1).

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

- Doses:

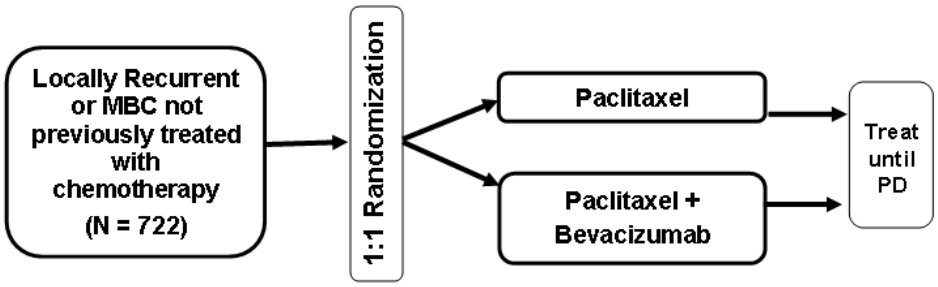
  Avastin: 15 mg/kg IV every 3 weeks

  Capecitabine: 2500 versus 1875 mg/m^2 IV twice daily

- Primary outcome measure: progression-free survival (PFS).
- Secondary outcome measures: objective response rate, duration of objective response, overall survival, and 1-year survival rate.
- Retrospective Independent Review Committee (IRC) assessment of PFS conducted.
- Study status: complete; data available (Miller et al. 2005).

2) E2100

E2100 Study Design



MBC = metastatic breast cancer; PD = progressive disease.

- Multicenter, randomized, open-label, controlled, Phase III trial that investigated the combination of paclitaxel + Avastin compared with paclitaxel alone.
- Conducted in the United States; sponsored by the National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP) and conducted by the Eastern Cooperative Oncology Group (ECOG) as an Intergroup study, in collaboration with nine other North American cooperative groups, including the 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).
- Patient population: patients who had not received chemotherapy for their HER2-negative locally recurrent or metastatic breast cancer.

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

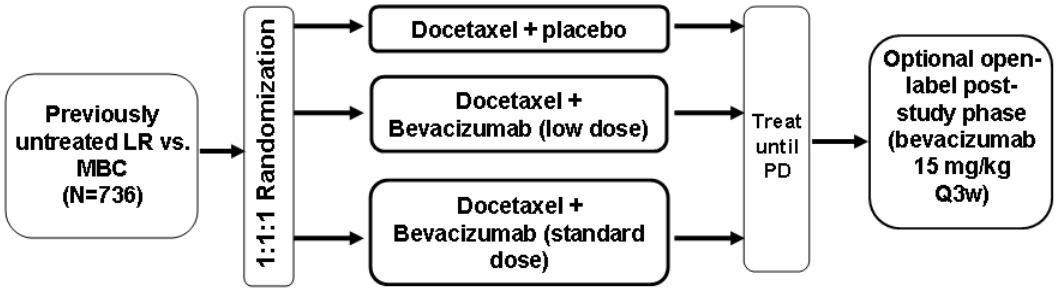
- Randomization: 1:1 to paclitaxel + Avastin or paclitaxel alone.
- Stratification factors: disease-free interval (≤ 24, > 24 months), previous adjuvant therapy (yes, no), estrogen receptor (ER) status (positive, negative, unknown), and number of metastatic sites (< 3, ≥ 3).
- Doses:

  Avastin: 10 mg/kg IV every 2 weeks

  Paclitaxel: 90 mg/m^2 IV infusion over 1 hour every week for 3 weeks followed by 1 week of rest
- Primary outcome measure: PFS (per protocol assessed by investigator; regulatory definition by IRC assessment).
- Secondary outcome measures: objective response rate, safety, and quality of life.
- Study status: complete; data available (Miller et al. 2007).

3) AVADO (BO17708)

AVADO Study Design



LR = locally recurrent; MBC = metastatic breast cancer; PD = progressive disease; Q3w = every 3 weeks.

- Multicenter, randomized, double-blind, placebo-controlled, Phase III trial that investigated the combination of docetaxel + Avastin (two doses) compared with docetaxel + placebo.
- Conducted outside the United States by Roche.
- Patient population: patients who had not received chemotherapy for their HER2-negative locally recurrent or metastatic breast cancer.

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

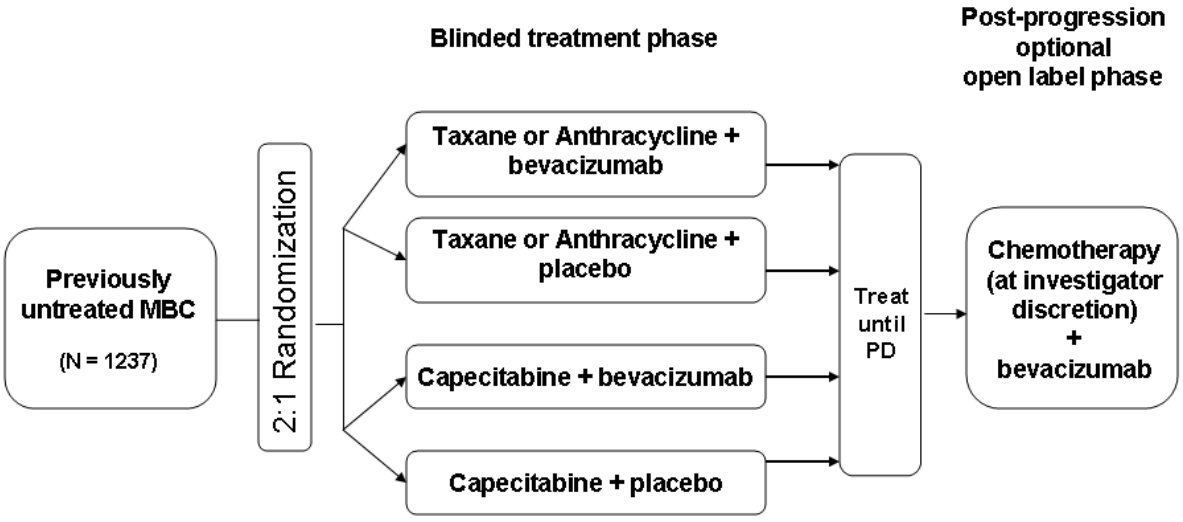
- Randomization: 1:1:1 to docetaxel + placebo, docetaxel + Avastin (low dose), or docetaxel + Avastin (standard dose).
- Stratification factors: region (Western Europe/Australia/Canada, Eastern Europe, Central and South America, East Asia/South Africa), previous adjuvant taxane therapy, time to relapse since last dose of (neo)adjuvant therapy, measurable disease (yes, no), and hormone receptor status (ER-negative and PgR-negative, ER- and/or PgR-positive).
- Doses:

  Avastin: 7.5 mg/kg IV every 3 weeks or 15 mg/kg IV every 3 weeks

  Docetaxel: 100 mg/m^2 IV
- Primary outcome measure: PFS (docetaxel + Avastin compared vs. docetaxel + placebo).
- Secondary outcome measures: objective response rate, overall survival, and 1-year survival rate.
- Study status: complete; data available (Miles et al. 2010).

4) RIBBON1 (AVF3694g)

RIBBON1 Study Design



MBC = metastatic breast cancer; PD = progressive disease.

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

- Multicenter, randomized, double-blind, placebo-controlled, Phase III trial that investigated the combination of chemotherapy + Avastin compared with chemotherapy + placebo. Chemotherapy choices were taxane (docetaxel or nab-paclitaxel), anthracycline (doxorubicin/cyclophosphamide, epirubicin/cyclophosphamide, 5-fluorouracil/doxorubicin/cyclophosphamide, 5-fluorouracil/epirubicin/cyclophosphamide), or capecitabine.
- Conducted in and outside the United States by Genentech and Roche.
- Patient population: patients who had not received chemotherapy for their HER2-negative locally recurrent or metastatic breast cancer.
- Randomization: 2:1 to chemotherapy + Avastin or chemotherapy + placebo.
- Stratification factors: disease-free interval ($\leq$ 12 months, $>$ 12 months since completion of adjuvant chemotherapy or surgery if no adjuvant chemotherapy), prior adjuvant chemotherapy (yes, no), number of metastatic sites (<3, ≥ 3), and choice of chemotherapy (taxane-based, anthracycline-based, capecitabine).
- Phases of study: blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase.
- Doses:

  Avastin: 15 mg/kg IV every 3 weeks

  Taxane:

  Docetaxel: 75–100 mg/m^2 IV every 3 weeks

  Nab-paclitaxel: 260 mg/m^2 IV every 3 weeks

  Anthracycline: Every 3 weeks, with a minimum of six cycles and a maximum of eight cycles of anthracycline (if maximum cumulative dose of anthracycline was reached, other components of chemotherapy could continue)

  AC (doxorubicin 50 or 60 mg/m^2, cyclophosphamide 500 or 600 mg/m^2) every 3 weeks

  FAC (5-FU 500 or 600 mg/m^2, doxorubicin 50 or 60 mg/m^2, cyclophosphamide 500 or 600 mg/m^2) every 3 weeks

  EC (epirubicin 90 or 100 mg/m^2, cyclosphosphamide 500 or 600 mg/m^2) every 3 weeks

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

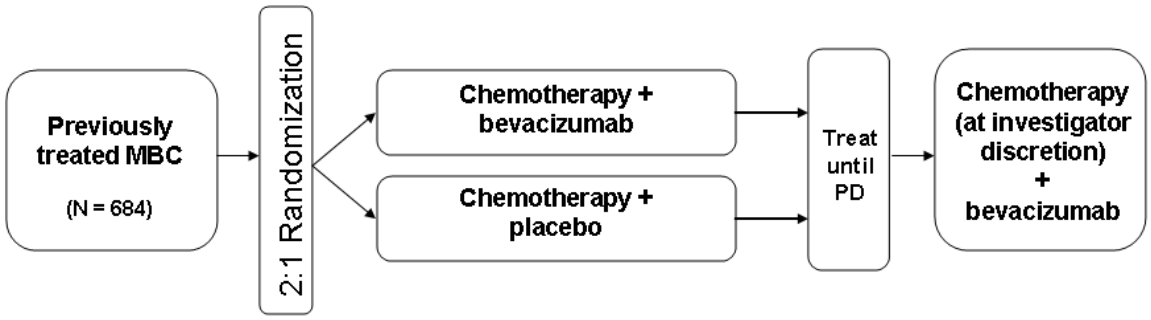
FEC (5-FU 500 or 600 mg/m^2, epirubicin 90 or 100 mg/m^2, cyclophosphamide 500 or 600 mg/m^2) every 3 weeks

Capecitabine: 1000 mg/m^2 oral twice daily on Days 1–14 of every 3-week cycle

- Primary outcome measure: PFS based on investigator assessments for 1) patients in the taxane/anthracycline + Avastin/placebo arm (comparison 1) and 2) patients in the capecitabine + Avastin/placebo arm (comparison 2).
- Secondary outcome measures: objective response rate, overall survival, 1-year survival rate, duration of objective response, and PFS based on IRC assessments.
- Study status: complete; data available (Robert et al. 2009).

5) RIBBON2 (AVF3693g)

RIBBON2 Study Design



MBC = metastatic breast cancer; PD = progressive disease.

- Multicenter, randomized, double-blind, placebo-controlled, Phase III trial that investigated the combination of chemotherapy + Avastin compared with chemotherapy + placebo. Chemotherapy choices were taxane (docetaxel or nab-paclitaxel), gemcitabine, capecitabine, or vinorelbine.
- Conducted in and outside the United States by Genentech.
- Patient population: patients who had not received chemotherapy for their HER2-negative locally recurrent or metastatic breast cancer.
- Randomization: 2:1 to chemotherapy + Avastin or chemotherapy + placebo.
- Stratification factors: chemotherapy regimen, interval from metastatic disease to first-line PD (< 6 months, ≥ 6 months), and ER and progesterone receptor (PgR) status (both negative, other).

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

- Phases of study: blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase.
- Doses:

  Paclitaxel: 90 mg/m^2 IV every week for 3 weeks followed by 1 week of rest, or 175 mg/m^2 IV every 3 weeks

  Nab-paclitaxel: 260 mg/m^2 IV every 3 weeks

  Docetaxel: 75–100 mg/m^2 IV every 3 weeks

  Gemcitabine: 1250 mg/m^2 IV on Days 1 and 8 of each 3-week cycle

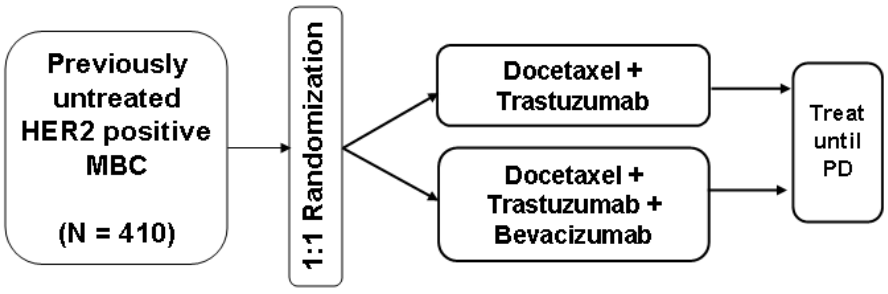
  Capecitabine: 1000 mg/m^2 IV orally twice daily on Days 1–14 of each 3-week cycle

  Vinorelbine: 30 mg/m^2 every week of each 3-week cycle

- Primary outcome measure: PFS based on investigator assessments for 1) patients in the taxane/anthracycline + Avastin/placebo arm (comparison 1) and 2) patients in the capecitabine + Avastin/placebo arm (comparison 2).
- Secondary outcome measures: objective response rate, overall survival, 1-year survival rate, duration of objective response, and PFS based on IRC assessments.
- Study status: complete; data available (Brufsky et al. 2009).

6) AVEREL (BO20231)

AVEREL Study Design



MBC = metastatic breast cancer; PD = progressive disease.

- Multicenter, randomized, open-label, controlled, Phase III trial investigating the combination of docetaxel/trastuzumab + Avastin compared with docetaxel/trastuzumab

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

- Conducted outside the United States by Roche.
- Patient population: patients with locally recurrent or metastatic HER2-positive breast cancer.
- Randomization: 1:1 to docetaxel/trastuzumab or docetaxel/trastuzumab + Avastin.
- Stratification factors: prior (neo)adjuvant taxane (yes, no), time to relapse since last dose of (neo)adjuvant chemotherapy (≤ 12 months, > 12 months since last dose of chemotherapy), trastuzumab as part of adjuvant treatment (yes, no), hormone receptor (ER/PgR) status (positive, negative), and measurable disease (yes, no).
- Doses:

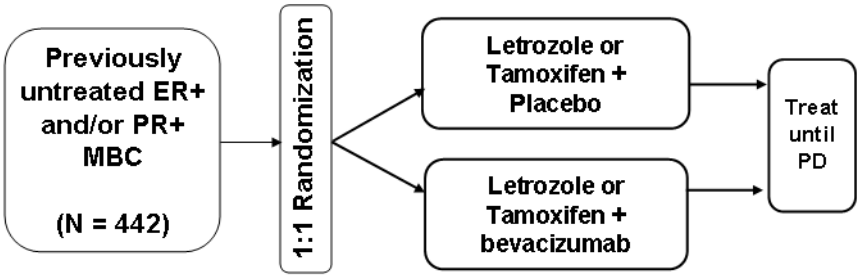
  Avastin: 15 mg/kg IV every 3 weeks

  Docetaxel: 100 mg/m^2 IV every 3 weeks

  Trastuzumab: 8 mg/kg IV loading dose and 6 mg/kg IV every 3 weeks maintenance dose
- Primary outcome measure: PFS (per protocol assessed by investigator; U.S. regulatory definition by IRC assessment).
- Secondary outcome measures: overall survival, best overall response, duration of objective response, time to treatment failure, quality of life, and safety.
- Study status: ongoing; enrollment complete.

7) CALGB 40503

CALGB 40503 Study Design



ER+ = estrogen receptor–positive; MBC = metastatic breast cancer; PD = progressive disease; PR+ = progesterone receptor-positive.

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

- Multicenter, randomized, double-blind, placebo-controlled, Phase III trial investigating the combination of endocrine therapy (letrozole or tamoxifen) + Avastin compared with endocrine therapy + placebo.
- Conducted in the United States; sponsored by NCI-CTEP and conducted by CALGB.
- Patient population: patients with ER- and/or PgR-positive advanced breast cancer.
- Randomization: 1:1 to hormone therapy + placebo or hormone therapy + Avastin.
- Stratification factors: endocrine therapy (letrozole, tamoxifen), measurable disease (yes, no), and last menstrual period (LMP; < 12 months since LMP or currently < 50 years old and had a hysterectomy with intact ovaries, > 12 months since LMP)
- Doses:

  Avastin: 15 mg/kg IV every 3 weeks

  Letrozole: 2.5 mg orally daily

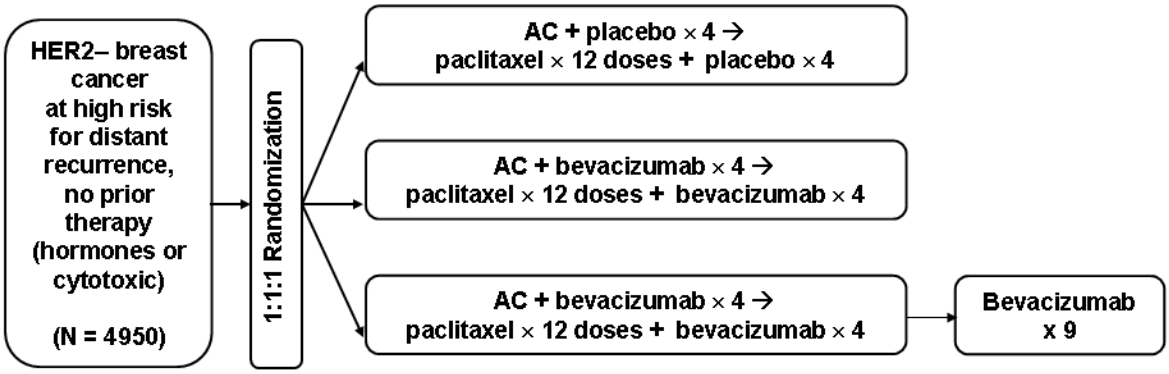
  Tamoxifen: 20 mg orally daily
- Primary outcome measure: PFS.
- Secondary outcome measures: proportion of patients progression-free at 6 and 12 months, PFS with letrozole + Avastin/placebo, PFS in tamoxifen + Avastin/placebo, objective response, duration of objective response, time to treatment failure, overall survival, and safety.
- Study status: ongoing.

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

Adjuvant Breast Cancer

1) E5103

E5103 Study Design



AC = doxorubicin + cyclophosphamide.

- Multicenter, randomized, double-blind, placebo-controlled, three-arm Phase III trial investigating the combination of sequential doxorubicin + cyclophosphamide (AC)/paclitaxel (T) + Avastin compared with AC/T + placebo.
- Conducted in the United States; sponsored by NCI-CTEP and conducted by ECOG.
- Patient population: patients with HER2-negative breast cancer who are at high risk for distant recurrence and who have not received prior therapy (hormones or cytotoxic chemotherapy).
- Randomization: 1:2:2 to the following arms

  AC + placebo (4 cycles) → T + placebo (4 cycles)

  AC + Avastin (4 cycles) → T + Avastin (4 cycles)

  AC + Avastin (4 cycles) → T + Avastin (4 cycles) + Avastin (9 cycles)
- Stratification factors: ER status (positive, other), lymph node–negative status (1–3+ lymph nodes, ≥4+ lymph nodes), and lumpectomy/whole breast radiation therapy (lumpectomy [accelerated partial breast irradiation pre-/post-chemotherapy], mastectomy [no radiation therapy planned], mastectomy [radiation therapy planned]).

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

- Doses:

  Avastin: 15 mg/kg IV every 3 weeks

  AC: choice of classic (every 3 weeks) or dose-dense (every 2 weeks) regimens

    Doxorubicin: 60 mg/m^2 IV every 3 weeks

    Cyclophosphamide: 600 mg/m^2 IV every 3 weeks

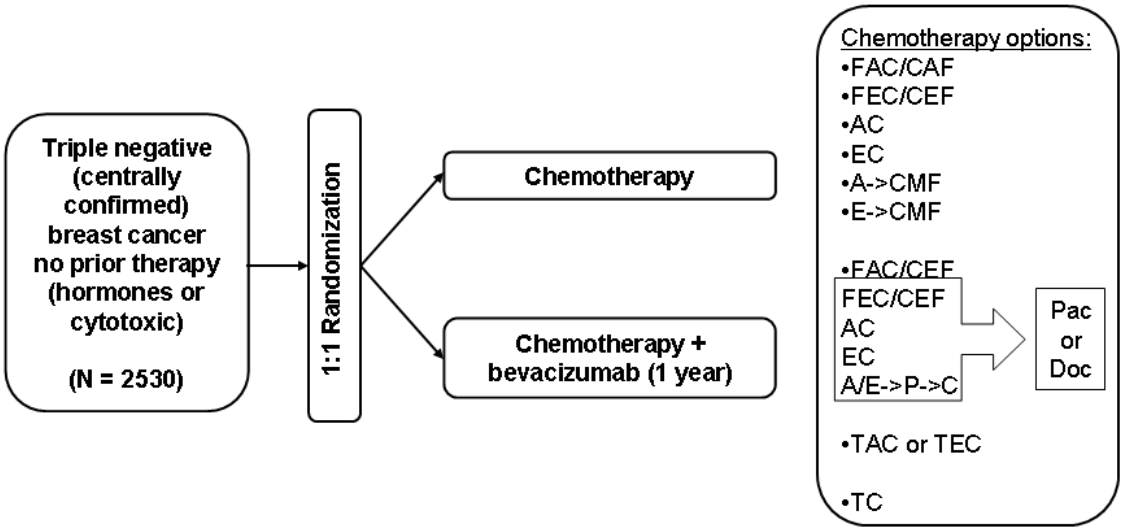
  Paclitaxel: 80 mg/m^2 IV every week

- Primary outcome measure: disease-free survival (DFS).
- Secondary outcome measures: DFS with short-term (20–24 weeks) versus long-term (50–54 weeks) Avastin therapy, overall survival, and safety.
- Study status: ongoing.

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

2) BEATRICE (BO20289)

BEATRICE Study Design



A = doxorubicin; AC = doxorubicin + cyclophosphamide; C = cyclophosphamide;
CEF = cyclophosphamide + epirubicin + 5-fluorouracil; CMF = cyclophosphamide + methotrexate + 5-fluorouracil;
Doc = docetaxel; E = epirubicin; EC = epirubicin + cyclophosphamide;
FAC/CAF = 5-fluorouracil + doxorubicin + cyclophosphamide; FEC = 5-fluorouracil + epirubicin + cyclophosphamide;
P and Pac = paclitaxel; TAC=docetaxel + doxorubicin + cyclophosphamide; TC = docetaxel + cyclophosphamide;
TEC = docetaxel + epirubicin + cyclophosphamide.

- Multicenter, randomized, open-label, controlled, Phase III trial investigating the combination of adjuvant chemotherapy + Avastin compared with adjuvant chemotherapy + placebo.
- Conducted in and outside the United States by Roche.
- Patient population: pre- and post-menopausal patients with triple-negative (ER-, PgR-, and HER2-negative), node-positive or -negative early primary invasive adenocarcinoma of the breast.
- Randomization: 1:1 to adjuvant chemotherapy + placebo versus adjuvant chemotherapy + Avastin (1 year).
- Stratification factors: number of axillary nodes involved (0, 1–3, ≥4), choice of systemic chemotherapy (taxane, non-taxane), hormone receptor status (ER- and PgR-negative, ER- and/or PgR-low), and surgery (breast conserving, mastectomy).

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

- Doses:

  Avastin: 5 mg/kg every week equivalent (10 mg/kg IV every 2 weeks or 15 mg/kg IV every 3 weeks)

  Chemotherapy: FAC/CAF, FEC/CEF, AC, EC, A→CMF, E→CMF

  Anthracycline-based regimens (FAC/CAF, FEC/CEF, AC, EC, A→CMF, E→CMF)

  Sequential anthracycline taxane regimens (FEC/CEF→paclitaxel or docetaxel, AC→paclitaxel or docetaxel, EC→paclitaxel or docetaxel, A/E→P→C→paclitaxel or docetaxel

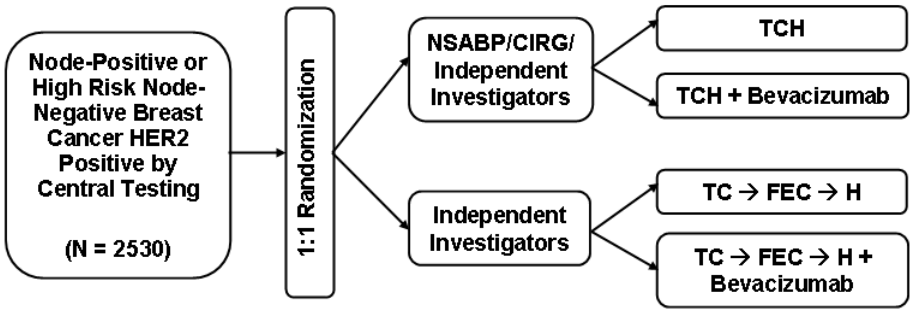
  Concurrent anthracycline/taxane regimens (TAC or TEC)

  Taxane regimens (TC)

- Primary outcome measure: invasive DFS.
- Secondary outcome measures: overall survival, breast cancer–free interval (BCFI), DFS, distant disease-free survival (DDFS), safety, and biomarkers.
- Study status: ongoing; enrollment complete.

3) BETH (BO20906)

BETH Study Design



FEC = 5-fluorouracil + epirubicin + cyclophosphamide; H = trastuzumab; TC = docetaxel + cyclophosphamide; TCH = docetaxel + carboplatin + trastuzumab.

- Multicenter, randomized, double-blind, placebo-controlled, Phase III trial investigating the combination of chemotherapy + Avastin compared with chemotherapy + placebo.

APPENDIX C (cont'd)
Overview of Study Designs in the Avastin Breast Cancer Clinical Development Plan

- Conducted in and outside the United States; sponsored in the United States by NSABP and outside the United States by Roche, in collaboration with the Cancer International Research Group (CIRG) and Genentech.
- Patient population: patients with HER2-positive node-positive, or high-risk node-negative breast cancer.
- Randomization: 1:1 to chemotherapy + trastuzumab (1 year) or chemotherapy + trastuzumab (1 year) + Avastin (1 year).
- Chemotherapy choices:

  TCH: docetaxel + carboplatin (every 3 weeks × 6 cycles) + trastuzumab (every 3 weeks × 1 year)

  TH→FEC→H: docetaxel + trastuzumab (every 3 weeks × 3 cycles)→5-FU, epirubicin, and cyclophosphamide (every 3 weeks × 3 cycles)→trastuzumab (every 3 weeks × 43 weeks)
- Stratification factors: number of positive nodes (0, 1–3, 4+) and hormone receptor status (ER- and/or PgR-positive, ER- and PgR-negative).
- Doses:

  Avastin: 15 mg/kg IV every 3 weeks

  Docetaxel: 75 mg/m^2 IV every 3 weeks × 6 cycles

  Carboplatin: AUC = 6 mg/mL/min IV every 3 weeks × 6 cycles

  Trastuzumab: 8 mg/kg IV for Cycle 1 followed by 6 mg/kg IV every 3 weeks × 5 cycles; 6 mg/kg IV every 3 weeks until 1 year following first trastuzumab dose regardless of any missed doses
- Primary outcome measure: Invasive DFS.
- Secondary outcome measures: DFS, overall survival, RFI, DRFI, cardiac toxicity, and safety.
- Study status: ongoing.

APPENDIX D
Regulatory History of Clinical Development Program of Avastin in Metastatic Breast Cancer

Genentech is the Sponsor of the Investigational New Drug (IND) Application for bevacizumab. Avastin (bevacizumab) was first approved by the U.S. Food and Drug Administration (FDA) as Avastin on 26 February 2004 for use in combination with intravenous (IV) 5-fluorouracil (5-FU)−based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon and rectum. The label was expanded to include the following indications:

- The second-line treatment of patients with colorectal cancer (20 June 2006)
- The first-line treatment, in combination with carboplatin and paclitaxel, of patients with unresectable, locally advanced, recurrent or metastatic non-squamous non–small cell lung cancer (11 October 2006)
- The treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer (22 February 2008 under the accelerated approval mechanism)
- The treatment of patients with glioblastoma with progressive disease following prior therapy (5 May 2009 under the accelerated approval mechanism)
- The treatment of patients with metastatic renal cell carcinoma in combination with interferon alfa (2 August 2009)

The accelerated approval for the first-line treatment of patients with metastatic breast cancer (MBC) in combination with paclitaxel was based on results from E2100, which showed a clinically meaningful and statistically significant improvement in progression-free survival (PFS). To further define the clinical benefit of combining first-line chemotherapy with Avastin, the data from two additional studies (AVADO and RIBBON1) are being submitted to support full approval for Avastin, in combination with various chemotherapy regimens, for the treatment of patients who have not received chemotherapy for their HER2-negative MBC.

E2100

Genentech received accelerated approval on 22 February 2008 for the use of Avastin in combination with paclitaxel for the treatment of patients who have not received chemotherapy for HER2-negative MBC on the basis of data from E2100.

APPENDIX D (cont'd)
Regulatory History of Clinical Development Program of Avastin in Metastatic Breast Cancer

The Subpart E Postmarketing Commitment (PMC) in the approval letter (see Table D-1) stipulated the following in order to further define the degree of clinical benefit to patients:

- To submit an efficacy supplement containing the final study reports for (including summary analyses and primary datasets) and revised labeling based on the results from the following studies:

  AVADO (BO17708), "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Docetaxel in Comparison with Docetaxel plus Placebo as First-Line Treatment for Patients with HER2-Negative MBC."

  RIBBON1 (AVF3694g), "A Multicenter, Phase III, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Patients with Previously Untreated MBC."

- Additionally, data (the Clinical Study Report, datasets and analyses) from the following studies are required to be submitted:

  RIBBON2 (AVF3693g), "A Phase III, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Treated Metastatic Breast Cancer"

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

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

AVADO

AVADO was conducted at clinical sites outside the United States. Table D-1 summarizes the regulatory interactions and correspondence between the FDA and Genentech regarding this study.

APPENDIX D (cont'd)
Regulatory History of Clinical Development Program of Avastin in Metastatic Breast Cancer

RIBBON1 (AVF3694g; Taxane/Anthracycline and Capecitabine Comparisons)

RIBBON1 was, in essence, two separate, independently powered comparisons (the taxane/anthracycline and capecitabine comparisons), conducted under the same protocol number.

RIBBON1 was conducted at sites within and outside the United States. Table D-2 summarizes the regulatory interactions and correspondences between the FDA and Genentech regarding this study.

Other Applicable Regulatory Interactions

The following interactions have occurred between the FDA and Genentech to discuss the PMC for submission of an efficacy supplement containing data from AVADO and RIBBON1:

- A Type C meeting was held on 7 October 2008 to discuss the proposals for integrated summaries of safety and efficacy for the efficacy supplement, during which the FDA requested that the data from AVADO and RIBBON1 be submitted in two separate sBLAs. Agreement was also reached on the provision of patient narratives, Case Report Forms (CRFs), datasets, and programs for both studies.
- A Type B meeting was held on 26 February 2009 to discuss the proposed contents of the supplements for AVADO and RIBBON1. At this meeting, the FDA highly recommended that Genentech provide updated overall survival data for each study in the submission of the respective sBLA.
- During an informal teleconference held on 6 March 2009 as follow-up to the Type B meeting, the FDA confirmed that the basis for conversion to full approval will be demonstrated improvement in PFS and evidence that survival is not impaired, and as a result, the applications must contain the results of the final analysis of overall survival in the supplement upon submission.

APPENDIX D (cont'd)
Regulatory History of Clinical Development Program of Avastin in Metastatic Breast Cancer

Table D-1
Summary of Key Regulatory Interactions for AVADO

Submission	Date
AVADO (BB-IND bevacizumab)	
FDA comments on Statistical Analysis Plan (in lieu of Type C meeting originally planned)	26 October 2007
Genentech submits amended Protocol and Statistical Analysis Plan	8 January 2008
Amended Statistical Analysis Plan	1 February 2008
FDA comments received on Statistical Analysis Plan	13 May 2008
Type C Meeting to discuss proposal for Integrated Summary of Safety/Integrated Summary of Efficacy (Avastin MBC sBLA—AVADO and RIBBON1)	7 October 2008
Type B to discuss contents of Avastin MBC sBLAs (AVADO and RIBBON1)	26 February 2009

APPENDIX D (cont'd)
Regulatory History of Clinical Development Program of Avastin in Metastatic Breast Cancer

Table D-2
Summary of Key Regulatory Interactions for RIBBON1

Submission	Date
RIBBON1 (BB-IND 7023; bevacizumab)	
New protocol	6 October 2005
FDA comments on the RIBBON1 protocol	29 December 2005
Genentech response to FDA comments on protocol	6 January 2006
Type B Meeting to discuss general development plan for Avastin	10 January 2006
Protocol submission (Amendment 1)	2 February 2006
Protocol submission (Amendment 2)	1 December 2006
Protocol submission (Amendment 3)	23 February 2007
Protocol submission (Amendment 4)	26 July 2007
Protocol resubmission (Amendment 4)	14 August 2007
Type C Meeting to discuss Statistical Analysis Plan	18 September 2007
Protocol submission (Amendment 5)	1 April 2008
Genentech submits revised Statistical Analysis Plan	23 April 2008
FDA comments received on Statistical Analysis Plan	10 July 2008
Genentech submits response to FDA Comments on Statistical Analysis Plan (10 July 2008)	26 January 2009
Type C Meeting to discuss proposal for Integrated Summary of Safety/Integrated Summary of Efficacy (Avastin MBC sBLA—AVADO and RIBBON1)	7 October 2008
Type B to discuss contents of Avastin MBC sBLAs (AVADO and RIBBON1)	26 February 2009

APPENDIX E
Summary of Results for the 7.5 mg/kg Arm of AVADO

AVADO included two treatment arms that combined docetaxel with Avastin at either 7.5 mg/kg or 15 mg/kg every 3 weeks. The trial was not designed to compare the two Avastin-containing arms, but rather each Avastin-containing arm was compared with the control arm. The 15 mg/kg dose corresponds to the standard 5 mg/kg per week equivalent currently indicated for MBC. Because E2100 and RIBBON1 evaluated only the Avastin dose equivalent to 15 mg/kg every 3 weeks, efficacy conclusions from AVADO are based only on patients treated at that dose and exclude the 248 patients enrolled in the 7.5 mg/kg arm. Safety results (presented in the main body of the briefing book) reflect data from all 2695 treated patients, including those who received Avastin in the 7.5 mg/kg arm of AVADO.

Key efficacy results for the 7.5 mg/kg arm are shown here for completeness (see Table E-1). Results for the 7.5 mg/kg arm appear to be numerically inferior to those for the standard 15 mg/kg arm.

APPENDIX E (cont'd)
Summary of Results for the 7.5 mg/kg Arm of AVADO

Table E-1
Efficacy Results from AVADO

	Doc + Placebo (n = 241)	Doc + Avastin7.5 (n = 248)	Doc + Avastin (n = 247)
PFS			
Patients with a PFS event	152 (63.1%)	135 (54.4%)	134 (54.3%)
PFS (months)			
HR [a] (relative to Doc + placebo) (95% CI)		0.70 (0.55, 0.90)	0.62 (0.48, 0.79)
Adjusted [b] p-value (relative to Doc + placebo)		0.0054	0.0003
Median [c]	7.9	8.7	8.8
Objective response rate			
Patients with measurable disease	207	201	206
Objective response rate	92 (44.4%)	111 (55.2%)	130 (63.1%)
Between-arm difference (95% CI) [d]		10.8% (0.9%, 20.7%)	18.7% (9.0%, 28.4%)
p-value (χ^2)		0.036	0.0001
Updated overall survival [e]			
Patients who died	108 (44.8%)	118 (47.6%)	116 (47.0%)
Overall survival (months)			
HR [a] (relative to Doc + placebo) (95% CI)		1.10 (0.84, 1.45)	1.00 (0.76, 1.32)
p-value (log-rank)		0.48	0.98
Median [c]	31.9	30.8	30.2

CI = confidence interval; Doc = docetaxel; HR = hazard ratio; PFS = progression-free survival.

Note: Patients in the Doc + Avastin7.5 arm received Avastin 7.5 mg/kg or until disease progression or toxicity; patients in the Doc + Avastin arm received Avastin 15 mg/kg every 3 weeks or until disease progression or toxicity.

[a] Estimated by stratified Cox regression. The strata were geographic region, prior adjuvant therapy and/or taxanes/time to relapse since last dose of adjuvant or neo-adjuvant chemotherapy, measurable disease, and hormone receptor status.

[b] Adjusted for multiple testing using closed test procedure.

[c] Median PFS and median overall survival were estimated from Kaplan−Meier curves.

[d] Approximate 95% CI for difference of two rates using Hauck−Anderson method.

[e] The cutoff for the updated analysis of overall survival was 30 April 2009 for AVADO.

APPENDIX F
Statistical Methodology

This appendix summarizes the statistical methods used for the analyses of results from the three studies in the first-line metastatic breast cancer (MBC) setting: E2100, AVADO, and RIBBON1. The data cutoffs and explanations of the populations used for the summary of safety and efficacy are also provided.

Summary of Statistical Methods for E2100, AVADO, and RIBBON1 as Pre-Specified in the Genentech-Authored Statistical Analysis Plans

Table F-1 summarizes the key differences in the pre-specified methods used in the analysis of efficacy endpoints in E2100, AVADO, and RIBBON1, as specified in each Genentech-authored Statistical Analysis Plan (SAP).

APPENDIX F (cont'd)
Statistical Methodology

Table F-1
Summary of Pre-Specified Methods for E2100, AVADO, and RIBBON1

Per the Genentech-Authored SAPs	E2100	AVADO	RIBBON1
Stratification factors used in stratified analyses	• DFI (≤24, >24 months) • Prior adjuvant chemo (yes, no) • Number of metastatic sites (<3, ≥3) • ER status (positive, negative, and unknown)	• Geographic region • Prior adjuvant therapy and/or taxanes/time to relapse since last dose of adjuvant or neo-adjuvant chemotherapy (yes, no) • Measurable disease (yes, no) • Hormone receptor status (positive, negative, and unknown)	• DFI (≤12, >12 months) • Prior adjuvant chemo (yes, no) • Number of metastatic sites (<3, ≥3) • Choice of chemo (T, Anth only)
Primary endpoint	PFS based on IRC assessment, censored at NPT; included on-study death only.	PFS based on investigator assessment, censored at NPT; included death any time.	PFS based on investigator assessment, censored at NPT; included death any time.
Primary analysis method for PFS	Stratified log-rank test.	Stratified log-rank test; p-values were adjusted using the closed test procedure for PFS.	Stratified log-rank test.
Primary analysis method for objective response	Cochran–Mantel–Haenszel test.	χ^2 test; p-values were adjusted using the hierarchical testing procedure.	Cochran–Mantel–Haenszel test; p-values were adjusted using the hierarchical testing procedure.
Primary analysis method for overall survival	Stratified log-rank test.	Stratified log-rank test; p-values were adjusted using the hierarchical testing procedure.	Stratified log-rank test; p-values were adjusted using the hierarchical testing procedure.
Primary analysis method for 1-year survival rate	z-test using Greenwood's formula for standard error.	z-test using Greenwood's formula for standard error; p-values were adjusted using the hierarchical testing procedure.	z-test using Greenwood's formula for standard error; p-values were adjusted using the hierarchical testing procedure.
Primary analysis method for quality of life	Summary of change from baseline in TOI at Week 17; Wilcoxon rank-sum test; zero imputation for patients who missed scores following PD or death.	Summary of change from baseline in TOI/FACT-B scores at Weeks 9, 15, and 33; for missing scores, the lowest observed score for a particular time point was used (lowest score imputation).	NA

Anth = anthracycline; DFI = disease-free interval; ER = estrogen receptor; FACT-B = Functional Assessment of Cancer Therapy—Breast; IRC=independent review committee; NA = not applicable; NPT = non-protocol-specified anti-cancer therapy; PD = progressive disease; PFS = progression-free survival; SAP = statistical Analysis Plan; T = taxane; TOI = Trial Outcome Index.

APPENDIX F (cont'd)
Statistical Methodology

Summary of Exploratory Pooled Analyses of Overall Survival

In addition to the analyses summarized in Table F-1, a post hoc exploratory analysis using pooled survival data from all three studies was performed to assess the affect on survival when Avastin was combined with chemotherapy. This analysis was performed only for the updated survival analysis. The Kaplan–Meier method was used to estimate overall survival, including estimates of median overall survival. The stratified log-rank test was used to compare the survival distributions between the Avastin-containing arm and the control arm. The hazard ratio for overall survival based on the pooled analysis was obtained using a stratified Cox model in which each individual study was used as a stratification factor.

Summary of Data Cutoffs

Per the Genentech-authored SAPs, two analyses of survival were to be performed for both AVADO and RIBBON1: the primary analysis at the time of the final PFS analysis (data cutoff of 31 October 2007 for AVADO and 31 October 2008 for RIBBON1) and one survival update for each study after unblinding (data cutoff of 30 April 2009 for AVADO and 23 February 2009 for RIBBON1). Only one analysis (data cutoff of 21 October 2006) was conducted for E2100.