Submission of Genentech, Inc.
in Response to the Food and Drug Administration's
Notice of Opportunity for a Hearing and Proposal to Withdraw Approval
of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel
for the First-Line Treatment of Patients with Metastatic Breast Cancer

Docket No. FDA-2010-N-0621

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LIST OF ABBREVIATIONS AND TERMS

CDER	Center for Drug Evaluation and Research
C.F.R.	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FACT-B	Functional Assessment of Cancer Therapy–Breast
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
GAO	Government Accountability Office
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
IB	Investigator Brochure
IND	Investigational New Drug
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MBC	metastatic breast cancer
N	footnote
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOOH	Notice of Opportunity for a Hearing
NS	not significant
ODAC	Oncologic Drugs Advisory Committee
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
REMS	Risk Evaluation and Mitigation Strategy
RPLS	reversible posterior leukoencephalopathy syndrome
SABCS	San Antonio Breast Cancer Symposium
sBLA	supplemental Biologics License Application
SPA	Special Protocol Assessment
T	table
TTP	time to progression
USPI	United States Package Insert
VEGF	vascular endothelial growth factor

INTRODUCTION

This submission responds to the FDA's Notice of Opportunity for a Hearing ("NOOH") regarding the Agency's proposal to withdraw approval of the metastatic breast cancer ("MBC") indication for Avastin® (bevacizumab). Together with the accompanying appendices and attachments, this document sets forth the data, analyses, and information on which Genentech, Inc. ("Genentech") intends to rely at a hearing to demonstrate why Avastin should remain an FDA-approved option for women in the United States who are facing this incurable disease. This document also explains Genentech's right to a hearing on FDA's proposed withdrawal.

EXECUTIVE SUMMARY

Metastatic breast cancer is an incurable disease that claims the lives of an estimated 40,000 women in the United States every year. Avastin paired with weekly paclitaxel delayed progression of MBC by a substantial 5.5 months and more than halved the risk of disease progression or death (progression-free survival, or "PFS"). Furthermore, Avastin has been combined with other chemotherapies and has resulted in improved PFS in each study that examined its effect in the first-line setting, showing the greatest effect when combined with paclitaxel.

On 22 February 2008, FDA granted accelerated approval to Avastin in combination with paclitaxel for the treatment of first-line HER2-negative MBC. This approval was based on a robust delay in tumor progression accompanied by a doubling of response rate in the E2100 study, a result FDA considered to be a clinical benefit in the context of patients facing this progressive, incurable disease. E2100, which was sponsored by the National Cancer Institute ("NCI"), compared Avastin plus weekly paclitaxel with paclitaxel alone. Since this approval, thousands of women with MBC have been treated with Avastin in the United States.

Genentech and its parent (F. Hoffmann–La Roche Ltd) conducted two additional studies of Avastin paired with chemotherapies other than paclitaxel. Genentech provided final PFS and interim overall survival ("OS") results of the AVADO study to FDA prior to the accelerated approval. AVADO and the other study, RIBBON1, each met their primary endpoints of improving PFS, but with a lesser magnitude of effect than was seen when Avastin was paired with paclitaxel in E2100. Although no new safety signals were identified in AVADO and RIBBON1, FDA now proposes to rescind Avastin's accelerated approval in combination with paclitaxel on the basis of

the lesser magnitude of the PFS effect in these two non-paclitaxel studies. Respectfully, Genentech disagrees with FDA's determination.

The robust improvement in PFS in the E2100 paclitaxel study is not invalidated by the two subsequent studies with alternate Avastin–chemotherapy combinations. Rather, the AVADO data with a non-paclitaxel partner, the new RIBBON1 data with non-paclitaxel partners, and additional new data on the combination of Avastin with paclitaxel suggest that the magnitude of benefit may vary with the particular chemotherapy used with Avastin. In aggregate, the data support Genentech's proposal to conduct a new confirmatory trial of Avastin with weekly paclitaxel, while maintaining the indication as a treatment option for patients under accelerated approval.

The following scientific, legal, and policy points support Genentech's position.

The Standard for Accelerated Approval Continues to Be Met

The accelerated approval standard calls for FDA to approve medications for serious and life-threatening diseases such as MBC where (i) the data establish a reasonable likelihood of clinical benefit and (ii) that benefit can be characterized by an additional study. Once this accelerated approval standard is met, withdrawal is not appropriate unless the data establish that there is no longer a reasonable likelihood of clinical benefit and no meaningful way to characterize the potential benefit further.
For Avastin, the standard for accelerated approval continues to be met. The data supporting a substantial benefit conferred by Avastin with weekly paclitaxel have not changed, and an additional study specifically testing this combination (as Genentech has proposed) can further characterize that benefit.

The Benefit–Risk Profile for Avastin with Weekly Paclitaxel Is Favorable

E2100 showed a substantial PFS benefit for Avastin with weekly paclitaxel. These data have been subject to rigorous independent confirmatory review, are statistically robust, and were accepted by FDA to support accelerated approval. The findings are also supported by other studies showing meaningful tumor control with Avastin plus weekly paclitaxel, as measured by median PFS.

AVADO and RIBBON1 do not invalidate E2100. AVADO and RIBBON1 each met their primary PFS endpoints, without detriment to OS. The lesser improvement in

PFS seen in these studies indicates that the choice of chemotherapy partner may influence the magnitude of benefit. As commonly arises in the field of oncology, the scientific basis for the observed differential effect of Avastin with paclitaxel is not yet understood. A leading hypothesis is that weekly paclitaxel is a potent, well-tolerated anti-tumor agent that when used with Avastin provides prolonged, beneficial exposure to the combined cytotoxic and anti-angiogenic therapies, relative to other combinations.

At the same time, AVADO and RIBBON1 did not identify new safety signals. The safety profile of Avastin is well characterized, and FDA acknowledged the extensive database of clinical trials and postmarketing safety data at the time the Agency granted accelerated approval. The common adverse effects associated with Avastin are clinically manageable, and the more serious risks are not common and are clearly set forth in the prescribing information. The potential risks of Avastin are not greater than those presented by other agents added to chemotherapy in the first-line MBC setting.

Expert scientific bodies, such as the Committee for Medicinal Products for Human Use ("CHMP") of the European Medicines Agency ("EMA") and the National Comprehensive Cancer Network ("NCCN"), affirmed the favorable benefit–risk profile for Avastin with paclitaxel on the basis of the same body of data reviewed by FDA. The continued clinical use of Avastin in MBC and the stated opinions of many leading breast cancer experts underscore the clinical benefit of Avastin and the views of the EMA's CHMP and the NCCN. FDA's contrary view of the data is at the other pole, rejecting even continued accelerated approval conditioned on the conduct of an additional study.

FDA's New Approval Standard in MBC Risks Deterring Drug Development

FDA's proposed withdrawal reflects a new approval standard for the first-line treatment of MBC—an improvement in median PFS similar to the substantial magnitude observed in E2100, or a demonstrated benefit in OS. FDA did not communicate this standard to Genentech prior to accepting or during its initial review of AVADO and RIBBON1. Moreover, the standard is not consistent with prior approvals in first-line MBC and will be difficult for novel therapies to meet in the future. This standard thus risks deterring development of new agents in an area of genuine unmet medical need.

FDA still has not articulated clearly what magnitude of improvement in median PFS or risk reduction in disease progression it will consider adequate to establish clinical benefit, thereby creating uncertainty for sponsors and potentially discouraging oncology innovation. Likewise, FDA has not articulated clearly the safety concerns that it considers to fall outside of acceptable standards for oncologists experienced in delivering chemotherapy and thereby to influence the required magnitude of improvement in median PFS. FDA's lack of clarity on approval standards is set against a backdrop where the difficulty in establishing OS benefit in first-line MBC is acknowledged to be greater than in the past for several reasons, including incremental improvements in PFS over multiple lines of therapy contributing to longer OS for these patients.

Clinician and Patient Choice Should Be Preserved

FDA, on the one hand, and the EMA, NCCN, and many breast cancer experts, on the other hand, have reached differing conclusions on the basis of the same dataset. This divergence of views demonstrates that the balance of benefits and risks falls within a zone where physicians and patients should be allowed to make informed treatment choices, based on individualized treatment determinations and clear disclosure of the available data in the approved labeling. FDA has suggested that even if the MBC indication is withdrawn, Avastin would continue to be available to patients because oncologists could use it for appropriate patients off-label. The potential for off-label use is not a legitimate justification for depriving women of appropriate access to Avastin. Additionally, withdrawal would jeopardize payer coverage and potentially bar patient access to therapy.

Withdrawal under these circumstances is inconsistent with the accelerated approval program and would be unprecedented. FDA has never withdrawn a drug from accelerated approval where the confirmatory trials met their agreed-upon primary endpoints and the studies revealed no new safety risk. It should not do so here.

Genentech Is Entitled to a Hearing

The governing FDA regulations provide without qualification for a public hearing. Additionally, a hearing is necessary to give full and fair consideration to the issues. There are fundamental differences between Genentech and FDA around the interpretation of the available data, the benefit–risk profile presented by Avastin (including consideration of data for other approved first-line therapies for MBC),

the consistency of FDA's proposed withdrawal with other Agency approval and withdrawal actions, and the broader implications of FDA's actions for the development of cancer medicines. In light of these fundamental differences, denial of a hearing would present serious due process concerns both for Genentech and for women with MBC.

In addition, this document and the accompanying materials contain substantial new information that FDA has not previously considered and that FDA's Oncologic Drugs Advisory Committee ("ODAC") did not consider when reviewing Avastin for MBC this past July. For example, Genentech is presenting the following:

- An assessment not considered by ODAC and considered in only preliminary form by FDA for why the data from E2100, AVADO, and RIBBON1, combined with additional data on Avastin plus weekly paclitaxel, suggest that the choice of chemotherapy used with Avastin influences the magnitude of effect
- A new statistical evaluation rebutting FDA's hypothesis that the results from E2100 are not meaningful because they reflect a "random high"
- An expanded presentation of how to interpret the safety database for Avastin
- A new comparison of the benefit–risk and overall value profile of Avastin plus paclitaxel relative to alternative therapies, such as Gemzar® (gemcitabine) plus paclitaxel
- The recent expert determinations of the EMA's CHMP and the NCCN, which were not available when ODAC convened in July and, in the case of the EMA's CHMP, was announced only concurrently with FDA's NOOH
- Recently stated expert views from leading breast cancer oncologists and new data on utilization patterns by treating clinicians that support the value of Avastin as a therapeutic choice
- An analysis not previously considered by ODAC or FDA of how the current data meet the legal and regulatory requirements for accelerated approval and are inconsistent with the standards and FDA precedent for withdrawal of accelerated approval
- An assessment of how FDA has changed the approval standards in first-line MBC, with accompanying statistical support and discussion to demonstrate the potential adverse implications for drug development

This information can be considered properly only in the public hearing to which Genentech is entitled under law, with live presentations and an opportunity for questioning by Genentech and FDA Center for Drug Evaluation and Research

("CDER") representatives. In addition, a public hearing would allow full consideration of the views expressed by any independent parties who submit materials to the docket.

At the hearing, Genentech seeks the participation of an objective advisory committee with substantial breast cancer expertise. The previous ODAC—whose initial vote against accelerated approval FDA overruled before recently adopting its subsequent vote to rescind accelerated approval—had modest breast cancer expertise, and FDA and the public would benefit from an advisory committee with greater experience in the specific disease state at issue here.

* * *

Genentech continues to stand behind the science of Avastin and the value that Avastin provides to MBC patients. The company requests a hearing because it believes women with this incurable disease are entitled to Avastin as an FDA-approved choice, and because FDA's proposed withdrawal raises broader implications for the development of cancer treatments that should be discussed in a public forum.

BACKGROUND[1]

Metastatic Breast Cancer

Breast cancer is the most commonly occurring cancer in women worldwide, and when it has metastasized, it is incurable, with over 90% of patients ultimately dying from their disease. It is estimated that more than 40,000 women in the United States died of MBC in 2009.[2]

The goals of MBC treatment are to achieve disease control, palliate symptoms, and prolong survival while maintaining quality of life.[3] Practically, given the absence of

[1] Genentech has presented much of this background information in prior FDA submissions. It is restated here to help ensure that those less familiar with the background will have the basic facts and history that underlie the remainder of the discussion in the submission.

[2] American Cancer Society, Inc., Breast Cancer Facts & Figures 2009–2010, *available at* http://www.cancer.org/acs/groups/content/@nho/documents/document/f861009final90809pdf.pdf (last visited 14 January 2011).

[3] Moulder S, Hortobagyi GN. Advances in the treatment of breast cancer. Clin Pharmacol Ther 2008;83(1):26–36; Cardoso F, Bedard PL, Winer E, et al. International Guidelines for Management of

curative therapy, this means that MBC patients require a succession of treatments over their remaining lifetimes.[4] The decision-making process involved in choosing a patient's treatment course and sequence is complex and requires individualized tailoring based on the tumor burden and related symptoms at a given time together with the underlying tumor biology (presence or absence of hormone receptors and human epidermal growth factor receptor 2 ["HER2"] amplification), a patient's age and medical co-morbidities, including those from prior cancer therapy, and the anticipated efficacy and safety of a proposed treatment.[5] Informed choice is an important element in the decision-making process, which involves a discussion of all of the above between physician and patient, factoring the patient's values and desires into the final therapeutic decision.[6]

Treatment options for patients with MBC include the use of single-agent or combination chemotherapy, hormonal therapy, and targeted biologic therapy. Prior exposure to and time to relapse after adjuvant combination chemotherapy, which typically includes the most active drugs, and HER2 and hormone receptor status have considerable impact on the selection and outcomes associated with treatment in the metastatic setting.[7] Effective treatments are available for patients whose tumors are HER2 positive and/or hormone receptive positive. However, the majority (70%–75%) of primary breast cancers do not express the HER2 gene,[8] and many patients with hormone receptor–positive tumors become resistant to hormonal

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Metastatic Breast Cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst 2009;101:1174–81; Gligorov J, Lotz JP. Optional treatment strategies in postmenopausal women with hormone-receptor-positive and HER2-negative metastatic breast cancer. Breast Cancer Res Treat 2008;112:53–66.

[4] Beslija S, Bonneterre J, Burstein HJ, et al. Third consensus on medical treatment of metastatic breast cancer. Ann Oncol 2009;20:1771–85.

[5] Chang J, Clark GM, Allred DC, et al. Survival of patients with metastatic breast carcinoma: importance of prognostic markers of the primary tumor. Cancer 2003;97:545–53; Telli ML, Carlson RW. First-line chemotherapy for metastatic breast cancer. Clin Breast Cancer 2009;9(Suppl 2):S66–S72; Beslija S, et al. Ann Oncol 2009.

[6] Cardoso F, et al. J Natl Cancer Inst 2009.

[7] Beslija S, et al. Ann Oncol 2009.

[8] Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177–82; Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989;244:707–12.

treatments. To date, there are no targeted therapies available for patients whose tumors do not express hormone receptors or are no longer eligible for hormonal therapy.[9] Thus, there is a heightened unmet medical need for this patient population.

Reflecting the heterogeneity of the disease, the landscape of treatments available for MBC is complex and has evolved over the last 30 years. Although FDA has approved a number of drugs for MBC, the range of options available to individual patients is, in fact, more limited. Many patients are treated with the most active agents (anthracyclines and taxanes) in the adjuvant setting, with the consequence that metastatic disease will already have developed some degree of resistance. There are also limitations to tolerance of therapy in the metastatic setting with respect to retreatment and further therapies. As a result, no single therapeutic approach to MBC has emerged that can be applied to all patients, and additional treatment options are crucial to provide physicians and patients with flexibility in their treatment strategy and decisions. The incurability of MBC demands that new treatment strategies continue to be explored.[10]

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").[11] VEGF initiates angiogenesis, a physiologic process that results in the formation and growth of new blood vessels. Inhibition of angiogenesis with targeted agents, both alone and in combination with other cytotoxic or targeted therapies, has been shown to be effective in delaying the growth of multiple tumor types, including breast cancer.

By acting directly on tumor vasculature, Avastin provides a complementary strategy when combined with cytotoxic agents that directly target the tumor cell. Avastin can

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[9] Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med 2011;62:233–47.

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

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

sensitize the tumor vasculature to chemotherapy-induced damage, which may result in tumor shrinkage. The anti-angiogenic activity of Avastin may then maintain 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 improve drug delivery to the tumor and limit hematogenous spread of malignant cells.[12] The anti-angiogenic, anti-vascular, and potential anti-metastatic activities of Avastin are central to its use in MBC.

Clinical Trials of Avastin in First-Line MBC

Genentech has sponsored a comprehensive clinical development plan for Avastin spanning 30 different tumor types in adjuvant and metastatic settings. On the basis of data generated by this broad research, Avastin has received FDA approval for the treatment of patients with metastatic colorectal cancer, advanced non-squamous, non–small cell lung cancer, and metastatic renal cell carcinoma, as well as accelerated approval for first-line metastatic HER2-negative breast cancer and relapsed glioblastoma.

Three Phase III studies were conducted to determine the effectiveness and safety of Avastin in the first-line MBC setting. Table 1 provides an overview of these three studies, each of which involved a different chemotherapy partner. The Phase III clinical trial that served as the basis for accelerated approval was E2100, a multicenter, randomized, open-label, controlled trial sponsored by the NCI Cancer Therapy Evaluation Program that investigated the combination of paclitaxel and Avastin compared with paclitaxel alone in patients who had not received chemotherapy in the metastatic setting for their HER2-negative MBC. Two additional Phase III studies, AVADO (BO17708) and RIBBON1 (AVF3694g), examined the effect of combining Avastin with other commonly used chemotherapeutic agents in first-line MBC. AVADO compared the combination of docetaxel and Avastin with docetaxel alone, and RIBBON1 consisted of two independently powered comparisons under a single protocol: Avastin and taxane/anthracycline compared with taxane/anthracycline alone (where the taxane was docetaxel or Abraxane® [nab-paclitaxel]), and Avastin and capecitabine

[12] Bagri A, Berry L, Gunter B, et al. Effects of anti-VEGF treatment duration on tumor growth, tumor regrowth, and treatment efficacy. Clin Cancer Res 2010;16(15):3887–900.

compared with capecitabine alone. The final PFS and interim OS results for AVADO were available and considered by FDA in the accelerated approval of Avastin for MBC.

Table 1

Overview of Phase III Trials of Avastin as First-Line Treatment for Metastatic Breast Cancer: E2100, AVADO, and RIBBON1[13]

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 [a]	Phase III, multicenter, randomized, double-blind, placebo-controlled trial 2:1 randomization	1) Taxane (docetaxel or Abraxane®) + 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.

[a] RIBBON1 consisted of two independently powered comparisons under a single protocol: the taxane/anthracycline comparison (622 patients) and the capecitabine comparison (615 patients).

PFS was the primary endpoint of all three studies, and the statistically significant PFS results for all three studies are presented in Table 2.

[13] Study Protocols for E2100, AVADO, and RIBBON1. *See also* Integrated Summary of Efficacy ("ISE"), in-text Table 1 at 14.

Table 2
Magnitude of Progression-Free Survival across Studies[14]

Study	Median PFS (months)		Difference in Median PFS (months)	Hazard Ratio (95% CI)
	Non-Avastin Arm	Avastin Arm		
E2100	5.8	11.3	5.5	0.48 (0.39, 0.61)
AVADO	7.9	8.8	0.9	0.62 (0.48, 0.79)
RIBBON1-T/Anth	8.0	9.2	1.2	0.64 (0.52, 0.80)
RIBBON1-Cap	5.7	8.6	2.9	0.69 (0.56, 0.84)

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

Other efficacy endpoints in the three studies included objective response rate ("ORR"), 1-year survival, and OS. These additional endpoints reinforced the findings of increased efficacy with the addition of Avastin. ORR was substantially increased in all three studies. One-year survival was also improved in E2100, AVADO, and the capecitabine comparison of RIBBON1.[15] The addition of Avastin to chemotherapy did not impair OS; all three studies showed no statistically significant difference in OS between the Avastin arms and the non-Avastin arms.[16] Tables 3, 4, and 5 summarize these data.

[14] ISE, in-text Table 34 at 123.

[15] The 1-year survival rate was 83.2% in the non-Avastin arm and 80.7% in the Avastin arm for the taxane/anthracycline comparison of RIBBON1 (p = NS). The 1-year survival rate was 74.8% in the non-Avastin arm and 81.0% in the Avastin arm for the capecitabine comparison of RIBBON1 (p = NS).

[16] The hazard ratio for OS was 1.11 (95% CI: 0.86, 1.43) for the taxane/anthracycline comparison of RIBBON1 (p = NS). The hazard ratio for OS was 0.88 (95% CI: 0.69, 1.13) for the capecitabine comparison of RIBBON1 (p = NS).

Table 3
Objective Response Rate across Studies[17]

Study	Objective Response Rate		Between-Arm Difference
	Non-Avastin Arm	Avastin Arm	
E2100	22.2%	49.8%	27.6% ($p<0.0001$)
AVADO	44.4%	63.1%	18.7% ($p=0.0001$)
RIBBON1-T/Anth	37.9%	51.3%	13.5% ($p=0.0054$)
RIBBON1-Cap	23.6%	35.4%	11.8% ($p=0.0097$)

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

Table 4
Analysis of One-Year Survival across Studies[18]

Study	One-Year Survival		Between-Arm Difference (95% CI)
	Non-Avastin Arm	Avastin Arm	
E2100	74.0%	81.4%	7.4% (1.3%, 13.5%)
AVADO	75.8%	84.3%	8.5% (1.3%, 15.6%)
RIBBON1-T/Anth	83.2%	80.7%	−2.6% (−9.0%, 3.9%)
RIBBON1-Cap	74.8%	81.0%	6.2% (−1.0%, 13.4%)

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

[17] ISE, in-text Table 34 at 123.

[18] ISE, in-text Table 34 at 123.

Table 5
Analysis of Overall Survival across Studies[19]

Study	Median Overall Survival (months)		Hazard Ratio (95% CI)
	Non-Avastin Arm	Avastin Arm	
E2100	24.8	26.5	0.87 (0.72, 1.05)
AVADO	31.9	30.2	1.00 (0.76, 1.32)
RIBBON1-T/Anth	NR	27.5	1.11 (0.86, 1.43)
RIBBON1-Cap	22.8	25.7	0.88 (0.69, 1.13)

CI = confidence interval; NR = not reached; RIBBON1-Cap = RIBBON1, capecitabine comparison; RIBBON1-T/Anth = RIBBON1, taxane/anthracycline comparison.

Regulatory History of Avastin in MBC

On 22 February 2008, FDA granted accelerated approval to Avastin for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer. This approval was based on E2100, which showed that Avastin in combination with paclitaxel resulted in a prolongation of PFS equivalent to a 52% reduction in the risk of disease progression or death compared with paclitaxel alone (hazard ratio ["HR"] of 0.48; $p < 0.0001$). Median PFS increased by 5.5 months, from 5.8 to 11.3 months. The risk reduction was consistent across patient subgroups and robust according to multiple sensitivity analyses. The PFS improvements were also confirmed by an independent and blinded review of the radiological and clinical data. The safety profile of Avastin in E2100 was consistent with previous Avastin experience, and no new safety signals were observed.

FDA's accelerated approval letter designated AVADO and RIBBON1 as Genentech's postmarketing study commitments. (Before FDA granted accelerated approval, Genentech had provided FDA final PFS and interim OS results from AVADO,[20] and RIBBON1 was ongoing.) Genentech completed these commitments promptly and on 16 November 2009 concurrently submitted (as FDA requested) two supplemental Biologics License Applications ("sBLAs") for AVADO and RIBBON1 requesting conversion of accelerated approval to full approval and expansion of the MBC indication to include use in combination with taxane-based,

[19] ISE, in-text Table 34 at 123.

[20] *See* Appendix B.

anthracycline-based, and capecitabine chemotherapy, based on the fact that both studies met their primary PFS endpoints with no new safety signals.

On 20 July 2010, ODAC reviewed the results of AVADO and RIBBON1 in context with the data from E2100. ODAC voted that the addition of Avastin to docetaxel, anthracyclines, or capecitabine did not have a favorable benefit–risk profile.[21] ODAC also voted that AVADO and RIBBON1 did not provide confirmatory evidence of the clinical benefit of Avastin in combination with paclitaxel, and that the indication for MBC should be removed from the Avastin label.[22] Although several ODAC members voiced support and desire for an additional trial, ODAC was not asked to vote on the possibility of maintaining the accelerated approval of Avastin with paclitaxel subject to additional study and/or labeling changes.

Genentech respectfully disagreed with the ODAC votes, and it formulated a targeted response to the concerns raised by ODAC. Genentech proposed that Avastin's MBC indication remain limited to use in combination with paclitaxel and that Genentech conduct a new study that would characterize further the effect of Avastin plus paclitaxel observed in E2100. The new study also would include a biomarker component to try to identify those women who are more likely to derive a more substantial benefit from Avastin.

On 16 December 2010, FDA issued Complete Response Letters to the sBLAs based on AVADO, RIBBON1, and RIBBON2,[23] the NOOH,[24] and a supporting memorandum from CDER (the "Decision Memorandum").[25] In the NOOH, FDA indicated that it determined withdrawal was necessary because the postmarketing clinical trials failed to verify clinical benefit and because the available data have not

[21] Minutes, 20 July 2010 ODAC at 4–5.

[22] Minutes, 20 July 2010 ODAC at 6–7.

[23] Genentech submitted the RIBBON2 sBLA on 16 July 2010 to seek expansion of the MBC indication for second-line use—specifically, for the use of Avastin in combination with taxanes, capecitabine, or Gemzar® in patients who have received prior chemotherapy in the MBC setting.

[24] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Michelle Rohrer, Ph.D., Vice President, Regulatory Affairs, Genentech, Inc. (16 December 2010).

[25] Memorandum from Dr. Richard Pazdur, Director, Office of Oncology Drug Products to Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research (15 December 2010), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ UCM237286.pdf (last visited 14 January 2011).

shown that Avastin is safe or effective under its conditions of use for MBC. On the same day, the EMA's CHMP confirmed that the benefits of Avastin in combination with paclitaxel outweigh its risks and that this combination remains a valuable treatment option for patients suffering from MBC.[26]

ARGUMENT

I. ACCELERATED APPROVAL SHOULD BE MAINTAINED BECAUSE THE CURRENT DATA CONTINUE TO SHOW A REASONABLE LIKELIHOOD OF CLINICAL BENEFIT.

Section 506(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and the regulations of FDA provide that the Agency may grant accelerated approval to a biologic product on the basis of an effect on a surrogate endpoint or a clinical endpoint that is "reasonably likely to predict clinical benefit."[27] Where this showing is made, the statute and the regulations contemplate the sponsor's undertaking additional studies to characterize further the clinical benefit of the product.[28] These provisions form the core of the accelerated approval standard: the available data show a reasonable likelihood of predicting clinical benefit, and additional study can further describe and confirm such benefit.

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[26] Press Release, European Medicines Agency, European Medicines Agency Completes Its Review of Avastin Used in Breast Cancer (16 December 2010), *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/12/news_detail_001166.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1 (last visited 14 January 2011). CHMP also concluded that the balance of benefits and risks of Avastin in combination with docetaxel is negative and that this combination should no longer be used in the treatment of breast cancer. *Id.*

[27] The statute states that FDA may approve a product "upon a determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit." FDCA § 506(b). FDA's regulations state that FDA may approve a product on the basis of trials "establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely . . . to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." 21 C.F.R. § 601.41.

[28] FDCA § 506(b)(2)(A) ("Approval of a fast track product … may be subject to the requirement[ ] that the sponsor conduct appropriate post-approval studies to validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint."); 21 CFR § 601.41 ("Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.").

Accelerated approval exists to address the vital public health need to encourage the development and expedite the availability of important new therapies for serious and life-threatening illnesses. As FDA explained in proposing its regulations, accelerated approval allows FDA to "approve new drugs for serious or life-threatening illnesses at the earliest possible point at which safety and efficacy can reasonably be established."[29] The Congress has similarly emphasized that

> The agency should be guided by the principle that expeditious approval of useful and safe new products enhances the health of the American people. Approving such products can be as important as preventing the marketing of harmful or ineffective products. This is especially true for people with life-threatening illnesses and for diseases for which alternative therapies have not been approved.[30]

This legal authority and statutory directive to make important new therapies available to patients even where the available data may not support a full approval must govern FDA's current evaluation of the data supporting first-line use of Avastin with paclitaxel for MBC. So long as the core conditions for accelerated approval continue to be met—namely, that the data for Avastin in combination with paclitaxel continue to be reasonably likely to predict clinical benefit, and this finding is amenable to further clinical testing—FDA should maintain the accelerated approval while an additional study is conducted.

Even where FDA determines that post-approval studies have not confirmed clinical benefit to the degree desired, withdrawal is not necessarily required or appropriate. As the United States Government Accountability Office ("GAO") set out in a 2009 report, "[a]lthough the regulations outline conditions under which FDA could utilize expedited withdrawal authority for drugs approved under the accelerated approval process . . . withdrawal is not required and the Agency has latitude in determining

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[29] 57 Fed. Reg. 13234, 13234 (15 April 1992). Congress in the legislative history to FDCA § 506 similarly noted that "the acceptance of effects on surrogate endpoints as evidence of efficacy can lead to more rapid availability of safe and effective drugs for Americans with serious or life threatening illnesses." Committee on Labor and Human Resources, Food and Drug Administration Modernization and Accountability Act of 1997, S. Rep. No. 105-43 (1 July 1997) at 44.

[30] S. Rep. No. 105-43 at 8 (quoting the Advisory Committee on the Food and Drug Administration chartered by the Secretary of HHS in 1989).

when to exercise this authority."[31] Withdrawal is appropriate only where the underlying standard for accelerated approval is no longer met—that is, there is no longer a reasonable likelihood of clinical benefit and there is no meaningful potential for additional study to characterize that benefit further.

FDA officials recently acknowledged this point, emphasizing that "[b]y definition, drugs approved under accelerated approval represent significant therapeutic advances for patients with serious and life-threatening illnesses."[32] Accordingly, when a confirmatory study does not affirm clinical benefit, withdrawal is not necessarily warranted; rather, the Agency's response "must be governed by the unique factors of the particular case."[33] FDA explained that a failure to confirm clinical benefit in a trial could reflect unforeseen limitations in trial design, or could overlook a subset of patients for whom the drug may be effective.[34] The Agency also noted the importance of considering what other options are available to patients.[35]

In this particular case, the current dataset supports maintaining accelerated approval of Avastin in combination with paclitaxel. In 2008, FDA determined that the data from E2100 met the standard for accelerated approval. AVADO and RIBBON1, which combined Avastin with other commonly used chemotherapy partners, were positive studies that met their primary PFS endpoints and confirmed a positive effect on tumor control. The lower magnitude of effect on median PFS in AVADO and RIBBON1 is an observation consistent with clinical experience that some chemotherapy agents (and their dose and schedule) yield different levels of clinical benefit.

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[31] U.S. Government Accountability Office, New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints, GAO-09-866 (September 2009) [hereinafter "GAO Report"] at 34.

[32] FDA's General Comments to the United States Government Accountability Office's Draft Report Entitled, New Drug Approval: FDA Needs to Enhance its Oversight of Drugs Approved on the Basis of Surrogate Endpoints (GAO-09-866) at 3 (appended to GAO Report at 61).

[33] *Id.*

[34] *Id.* at 3–4.

[35] *Id.* at 3.

Genentech viewed AVADO and RIBBON1 as confirming a clinical benefit of Avastin in MBC. ODAC and FDA came to a contrary conclusion based on the lower magnitude of effect on median PFS in these trials. However, even if FDA views AVADO and RIBBON1 as failing to confirm the clinical benefit of Avastin in MBC for purposes of conversion to full approval, Genentech respectfully submits that this view does not justify the opposite conclusion of withdrawal.

As set forth more fully in the following section, AVADO and RIBBON1 do not negate the clinical benefit that FDA recognized when it granted accelerated approval based on the substantial PFS effect observed with Avastin plus paclitaxel. Rather, the data from these additional studies are consistent with an unforeseen limitation in the designs of the confirmatory trials—namely, the degree of difference in the magnitude of clinical benefit when Avastin is used in combination with paclitaxel versus with other chemotherapies. As such, the potential exists to characterize further the benefit observed in E2100 with an additional study specifically testing the combination of Avastin with weekly paclitaxel. Thus, the totality of the current data continues to meet the letter and spirit of the accelerated approval provisions of the FDCA and FDA's regulations. The data justify the continued availability of Avastin plus paclitaxel to address the immediate needs of women with MBC, who can derive clinical benefit while an additional study is conducted to characterize this clinical benefit more fully.

II. THE CURRENT DATA ESTABLISH A FAVORABLE BENEFIT–RISK PROFILE FOR AVASTIN IN COMBINATION WITH PACLITAXEL.

E2100 showed a substantial and clinically meaningful increase in PFS, as measured by the hazard ratio of 0.48 and median PFS benefit of 5.5 months, when Avastin was added to weekly paclitaxel. Importantly, the PFS improvements were confirmed by an independent and blinded review of the radiological and clinical data. Secondary E2100 endpoints underscored this strong activity, and the subsequent data from independent studies with the Avastin and paclitaxel combination are consistent with the PFS results observed in E2100. On the basis of these data, the grounds for maintaining accelerated approval of Avastin plus paclitaxel remain.

The Decision Memorandum reflects the reasoning that AVADO and RIBBON1, which involved chemotherapy partners other than paclitaxel, invalidate E2100's findings with Avastin and paclitaxel or show the study to be a spurious outlier.

Respectfully, the data do not support this conclusion. AVADO and RIBBON1 confirmed E2100's showing of an effect in MBC by replicating the statistically significant PFS findings that E2100 generated and that led FDA to grant accelerated approval. Their main variance from E2100 is their lesser *magnitude* of PFS effect. Rather than invalidating E2100, however, this different magnitude suggests that the chemotherapy partner for Avastin influences the magnitude of its effect.[36]

Stated differently, it is inappropriate to grant accelerated approval for Avastin in combination with paclitaxel (and not with other chemotherapy partners), only then to revoke that approval because of subsequent data involving *different* chemotherapies. This is especially true when the subsequent data show a consistent positive effect of Avastin, but at a lesser magnitude of effect on median PFS with chemotherapies other than paclitaxel.

Faced with this same dataset and with the consistent safety profile of Avastin (discussed further below), other scientific decision-makers have affirmed the benefit–risk profile of Avastin plus paclitaxel. FDA's position lies on the other end of the spectrum. FDA's judgment is that the benefit–risk profile of Avastin and paclitaxel is now so plainly unfavorable—on the basis of data involving Avastin and other chemotherapy partners—that Avastin should not remain available as an approved option for any woman with MBC, not even under accelerated approval. Given the showing of a likely differential benefit for Avastin with weekly paclitaxel, a more measured determination is that the available data support accelerated approval.

A. THE DATA SHOW A SUBSTANTIAL TREATMENT EFFECT FROM AVASTIN.

1. The E2100 Data Are Robust.

Avastin in combination with paclitaxel was granted accelerated approval for use in MBC on the basis of E2100. E2100 was a randomized, controlled, well-conducted, Phase III trial that enrolled over 700 patients from centers predominantly in the United States. As a result, E2100 reflects the demographics, co-morbidities, and standards of care associated with first-line MBC in this country. E2100 was

[36] The data from Study AVF2119g also do not negate the findings of E2100, as suggested by FDA. AVF2119g was also a non-paclitaxel trial comparing Avastin plus capecitabine with capecitabine alone. In addition, the trial was conducted in a different treatment context: heavily pretreated/refractory MBC defined by pre-treatment with anthracyclines and taxanes.

sponsored by the NCI Cancer Therapy Evaluation Program and conducted by the Eastern Cooperative Oncology Group ("ECOG") in collaboration with nine other cooperative groups. ECOG is one of the largest cancer research organizations in the United States, and its network includes experienced researchers, physicians, and health care professionals at public and private institutions across the country. The results of E2100 were subjected to rigorous independent confirmatory review[37] with support from Genentech, and the ECOG dataset was peer-reviewed and published in the *New England Journal of Medicine*.[38]

The intent-to-treat analysis of the E2100 data showed a statistically significant reduction in the risk of disease progression or death ($HR = 0.48$; $p < 0.0001$), and the magnitude of increased median PFS—5.5 months (from 5.8 to 11.3 months)—was substantial. Notably, as shown in Table 6, the PFS benefit conferred by Avastin exceeded the magnitude of PFS benefit observed in other Phase III trials in first-line MBC.

[37] Gray M, Bhattacharya S, Bowden C, et al. Independent review of E2100: a Phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol 2009;27:4966–72.

[38] Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New Engl J Med 2007;357:2666–76.

Table 6
Contemporary Phase III Studies in First-Line MBC with Positive PFS/TTP

Publication	Regimen	PFS/TTP Median (months)	Difference in Median PFS/TTP (months)
Sledge et al. 2003 (n=739)	AT vs. T	8.2 vs. 6.0	2.2
	AT vs. A	8.2 vs. 6.3	1.9
Jassem et al. 2001 (n=267)	AT vs. FAC	6.2 vs. 8.3	2.1 [a]
Albain et al. 2008 (n=599)	T vs. GT	4.0 vs. 6.1	2.1 [a]
Bontenbal et al. 2005 (n=216)	FAC vs. Dox+Doc	6.6 vs. 8.0	1.4
Nabholtz et al. 2003 (n=429)	Doc+Dox vs. AC	7.3 vs. 8.6	1.3 [a]
Lueck et al. 2006 (n=340)	EP vs. XT	9.2 vs. 10.4	1.2
Mackey et al. 2002 (n=484)	FAC vs. TAC	7.2 vs. 7.7	0.5
Carmichael et al. 2001 (n=705)	EC vs. ET	6.7 vs. 6.5	0.2
Zielinski et al. 2005 (n=259)	Gem, Epi, T vs. FEC	9.0 vs. 9.1	0.1
Biganzoli et al. 2002 (n=275)	AT vs. AC	6 vs. 6	0

A=doxorubicin; AC=doxorubicin+cyclophosphamide; AT=doxorubicin+paclitaxel;
EC=epirubicin+cyclophoshamide; EP=epirubicin+paclitaxel; Epi=epirubicin;
ET=epirubicin+paclitaxel; Doc=docetaxel; Dox=doxorubicin;
FAC=5-fluorouracil+doxorubicin+cyclophosphamide;
FEC=5-fluorouracil+epirubicin+cyclophosphamide; Gem=gemcitabine;
GT=gemcitabine+paclitaxel; PFS=progression-free survival; T=paclitaxel;
TAC=docetaxel+doxorubicin+cyclophosphamide; TTP=time to disease progression;
XT=capecitabine+paclitaxel.

Note: All studies were open label.

[a] As assessed by an independent review facility.

Other E2100 efficacy endpoints reinforce the benefits of Avastin plus paclitaxel. ORR more than doubled, from 22% to 50%. Although an improvement in 1-year survival was observed, E2100 did not show a statistically significant impact on OS. The OS hazard ratio of 0.87 (p=0.14), median survival of 26.5 months versus 24.8 months, and exploratory 1-year survival rate of 81% versus 74% (p=0.017)

favored the Avastin arm in the study, however.[39] The lack of a statistically significant effect on OS is not surprising, as the trial was not powered for OS and therefore had only limited power, at 25%, to detect an increase of 3 months at the median. In addition, the lack of a significant effect on OS may reflect the methodological challenges involved in assessing an OS impact in the first-line setting, as discussed further in Section III.C. FDA granted accelerated approval based on E2100 notwithstanding the lack of a proven superior OS benefit.

Specifically, in 2008 FDA determined that the PFS benefit observed in E2100 was a sufficient basis for accelerated approval. Although FDA initially had questions about the reliability of the E2100 results because of the open-label design, Genentech addressed questions about potential systematic bias through extensive independent third-party review. At the 5 December 2007 ODAC meeting, Medical Reviewer Dr. Lee Pai-Scherf stated that FDA did not have sufficient experience with independent radiological review such that it was difficult to interpret the discordance rate between investigator and independent radiologist assessment.[40] Subsequent experience in MBC has shown similar discordance rates for agents that received full approval.[41] For example, the Tykerb® (lapatinib) filing showed a discordance rate of 29%, clearly in the same range as the 24% discordance rate in E2100.[42] Importantly, no systematic bias was seen in the primary endpoint analysis of E2100 for the investigator and independent radiology reviews (hazard ratios of 0.48 and 0.42, respectively).

Multiple sensitivity analyses accounting for factors including non-protocol cancer therapy, missing scans, and early study discontinuation, all affirmed the robustness of the PFS benefit in E2100.[43] Ultimately, FDA determined that the PFS benefit in the study justified accelerated approval, and the ODAC that advised FDA on this

[39] ISE, in-text Table 34 at 123.

[40] Transcript, 5 December 2007 ODAC at 133.

[41] Tykerb® Summary Basis of Approval, Ixempra® Summary Basis of Approval; Gray M, et al. J Clin Oncol 2009.

[42] Tykerb® Summary Basis of Approval.

[43] Genentech, Inc., Briefing Book, 5 December 2007 ODAC, in-text Table 16.

decision noted that the PFS benefit was "clinically meaningful."[44] As Dr. Richard Pazdur, Director, Office of Oncology Drug Products, stated at the time in explaining FDA's approval decision, "[i]n this case, a robust delay in progression accompanied by a doubling of response rate was considered a benefit to patients facing a progressive, incurable disease."[45] Dr. Pazdur added that multiple sensitivity and subgroup analyses corroborated the drug's effect, "[t]here was close agreement between investigator-assessed endpoints … and the independent radiographic facility (IRF)," and analyses of "missing data" did not raise concerns about systematic bias.[46] He acknowledged that "the E2100 trial was statistically robust. We are confident in an effect on the primary endpoint."[47]

In its Decision Memorandum, FDA now has raised the possibility that the magnitude of the PFS benefit observed in E2100 was an artifact of the pre-specified interim analysis of PFS.[48] This assertion of a "random high" is not a proper basis for impeaching the results of E2100 for the following three reasons: (i) the results of E2100 were derived from the first interim analysis in a well-planned and rigorously conducted analysis plan and thus do not require adjustment for bias,[49] (ii) the interim results were based on a robust number of PFS events and a long follow-up period, comparable to the number of events and follow-up in the final analyses of AVADO and the two RIBBON1 comparisons,[50] and (iii) when more PFS events accrued, the results did not change (after 21 months of additional follow up and 200 more PFS events, the magnitude of the PFS benefit persisted, i.e., a median PFS benefit of

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[44] Transcript, 20 July 2010 ODAC at 13 ("The magnitude of benefit attributed to the addition of Avastin to paclitaxel was considered to be clinically meaningful in light of Avastin's toxicity by several of the ODAC participants.").

[45] PFS Is a Benefit 'in the Right Context,' Pazdur Says in Q&A on Avastin Approval, The Cancer Letter, 29 February 2008.

[46] *Id.* at 3.

[47] *Id.* at 4.

[48] Decision Memorandum at 5 ("[I]t is possible that the magnitude of effect observed in the E2100 based on the interim analysis represents a random high and that the true effect is more consistent with the smaller effect seen in the other trials.").

[49] Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Boca Raton: Chapman and Hall/CRC, 2000:186.

[50] Scientific discussion paper: Response to the issue raised by FDA that the E2100 result may represent a "random high," Table 1 at 4.

5.9 months based on ECOG's per-protocol analysis, as reported in the *New England Journal of Medicine*).[51]

2. The E2100 Results Are Supported by Additional Studies of Avastin with Paclitaxel.

The results of E2100 find support in subsequent studies of Avastin plus paclitaxel. Sponsors independent of Genentech have studied Avastin plus paclitaxel in a range of Phase II trials. These trials were smaller in size and yielded results with relatively wide confidence intervals individually. Nonetheless, taken together the studies as a group show consistent median PFS for Avastin plus paclitaxel, in line with the median PFS of 11.3 months observed in E2100. In these studies, median PFS for the Avastin plus paclitaxel combinations were 11.5, 12.9, and 13.5 months.[52,53] The similarity in median PFS results in multiple studies conducted by independent investigators support the conclusion that the E2100 results are robust and *do not* represent an outlier.

In addition to these independent studies, Genentech's parent company (F. Hoffmann–La Roche) sponsored a Phase IV, open-label study (ATHENA) in the postmarketing setting to assess further the safety and efficacy of Avastin in MBC.

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[51] Miller K, et al. New Engl J Med 2007. This 5.9-month median PFS difference reflects no censoring for non-protocol therapy, whereas the 5.5-month median PFS difference reflected censoring for non-protocol therapy. The sensitivity analysis of the 5.5-month median PFS difference that did not censor for non-protocol therapy showed a median PFS difference of 5.1 months.

[52] Mackey J, Hurvitz S, Crown J, et al. CIRG-TORI 010: 10-month analysis of a randomized phase II trial of motesanib plus weekly paclitaxel as first line therapy in HER2-negative metastatic breast cancer [abstract]. SABCS 2009:abstract 47; Masuda N, Aogi K, Ohno S, et al. Phase II study of bevacizumab (Bev) combined with weekly paclitaxel (wPac) as first-line therapy for Japanese patients (pts) with HER2-negative metastatic breast cancer (MBC) [abstract]. Proc Am Soc Clin Oncol 2010:abstract 1121; Rugo HS, Campone M, Amadori D, et al. Randomized phase II study of weekly versus every 3 week ixabepilone plus bevacizumab (ixa/bev) versus paclitaxel plus bev (pac/bev) as first-line therapy for metastatic breast cancer (MBC): final results [abstract]. Proc Am Soc Clin Oncol 2010:abstract 1040.

[53] Pfizer conducted a fourth recent independent study, comparing sunitinib (Sutent®) plus paclitaxel to Avastin plus paclitaxel. The study was stopped early after it showed superiority in the Avastin arm, at which point the median PFS in that arm was 9.2 months, with 30% of the required PFS events having occurred. Pfizer, Inc., A phase 3 study of su011248 in combination with paclitaxel versus bevacizumab with paclitaxel in the first-line advanced disease setting in patients having breast cancer, Protocol No. A6181094 (January 2010), *available at* http://www.clinicalstudyresults.org/documents/company-study_10195_0.pdf (last visited 14 January 2011).

This study enrolled 2296 patients in 37 countries and examined Avastin in combination with paclitaxel or docetaxel (and other chemotherapies, with the exception of anthracyclines, if taxanes were not the preferred chemotherapy).[54] The data demonstrated median time to progression ("TTP") of 10.6 months in the 325 patients receiving Avastin in combination with weekly paclitaxel, approaching the median PFS of 11.3 months observed in the Avastin arm of E2100 and further supporting that the E2100 results do not represent an outlier.[55]

No data subsequent to E2100 contradict these findings. The available data on Avastin plus paclitaxel in first-line MBC all suggest a clinically meaningful effect for patients.

B. THE DATA FROM AVADO AND RIBBON1 CONFIRM AVASTIN'S ACTIVITY IN MBC AND SUGGEST THAT THE CHEMOTHERAPY PARTNER INFLUENCES THE MAGNITUDE OF EFFECT.

AVADO and RIBBON1 met their primary PFS endpoints with a high degree of statistical significance, with hazard ratio estimates of 0.62 to 0.69 and increases in median PFS ranging from 0.9 months to 2.9 months.[56] Other endpoints measured in AVADO and RIBBON1 reinforced the findings of increased efficacy. Objective response rate was improved in both studies (see Table 3). One-year survival was also improved in AVADO and numerically favorable in the RIBBON1 capecitabine comparison.[57] These findings confirm that Avastin is active in MBC and reduces the risk of disease progression when combined with standard chemotherapy.

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[54] Smith IE, Pierga JY, Biganzoli L, et al. First-line bevacizumab plus taxane-based chemotherapy for locally recurrent or metastatic breast cancer: safety and efficacy in an open-label study in 2251 patients. Ann Oncol Advance Access. Epub 5 September 2010.

[55] *See* Appendix C. Genentech has not previously provided these data to FDA.

[56] In contrast to hazard ratios, which reflect all available information, medians reflect a single data point. Thus, for example, in AVADO the hazard ratio of 0.67 demonstrates a stronger treatment effect than the delta of the medians of 0.9 months. *See* Table 2, *supra*.

[57] The 1-year survival rate was 83.2% in the non-Avastin arm and 80.7% in the Avastin arm for the taxane/anthracycline comparison of RIBBON1 (p=NS). The 1-year survival rate was 74.8% in the non-Avastin arm and 81.0% in the Avastin arm for the capecitabine comparison of RIBBON1 (p=NS). *See* Table 4, *supra*.

As with E2100, both AVADO and RIBBON1 showed no statistical differences when OS in the Avastin arm was compared with OS in the non-Avastin arms.[58] Both studies allowed for patients randomized to the control arm to receive Avastin after first progression, which was extensively used by investigators and patients (40%–62% crossover). A pooled analysis of all three studies also showed no impairment of OS, with an estimated hazard ratio for OS of 0.97 (95% CI: 0.86, 1.08; p=0.56) favoring the Avastin-containing arm.[59] Kaplan–Meier estimates based on the pooled analysis showed an early separation of the survival curves in favor of the Avastin arm. *See* Figure 1.[60]

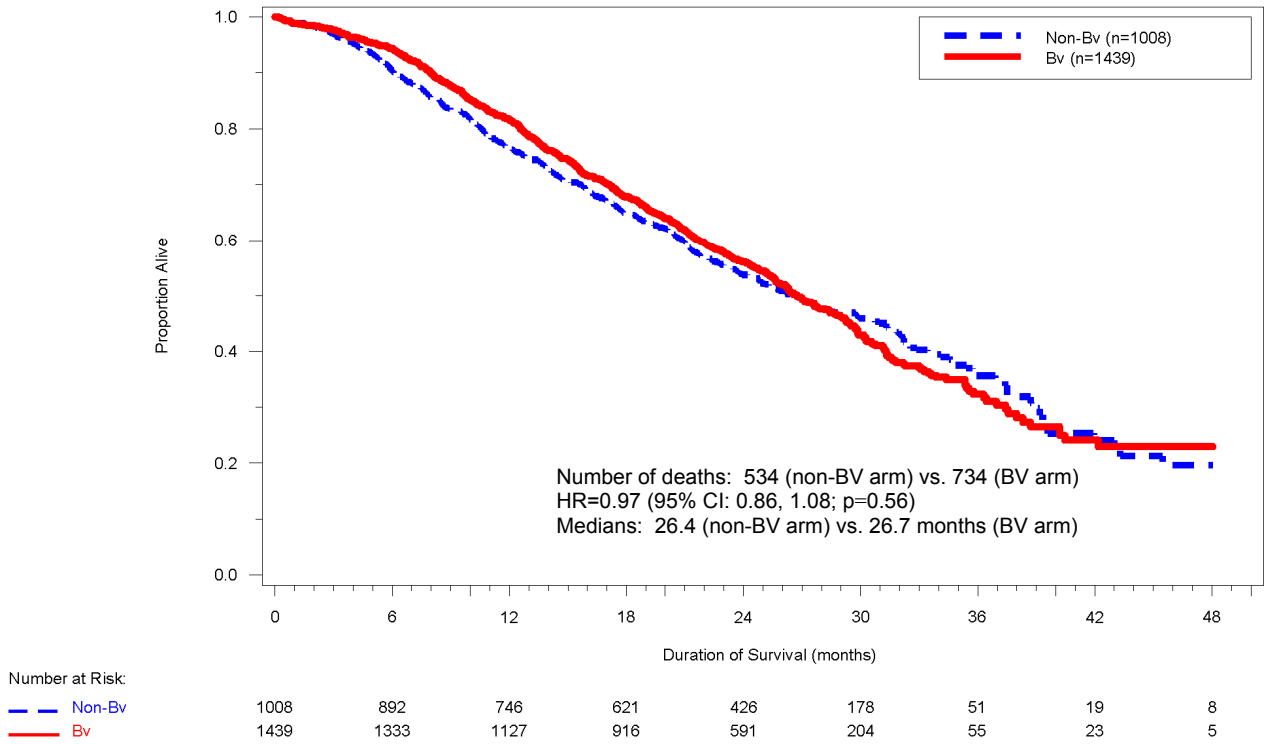
[58] The hazard ratio for OS was 1.11 (95% CI: 0.86, 1.43) for the taxane/anthracycline comparison of RIBBON1 (p=NS). The hazard ratio for OS was 0.88 (95% CI: 0.69, 1.13) for the capecitabine comparison of RIBBON1 (p=NS). *See* Table 5, *supra*.

[59] ISE, in-text Table 34 at 123.

[60] ISE, in-text Figure 18 at 96.

Figure 1

Kaplan–Meier Curves for Overall Survival Based on Survival Data Pooled across E2100, AVADO, and RIBBON1: Randomized Patients



Number at Risk:									
Non-Bv	1008	892	746	621	426	178	51	19	8
Bv	1439	1333	1127	916	591	204	55	23	5

BV=bevacizumab (Avastin); Cap=capecitabine; CI=confidence interval; Doc=docetaxel HR=hazard ratio; Pac=paclitaxel; PL=placebo; T/Anth=taxane/anthracycline.

Note: Data cutoff dates were 21 October 2006 (the data cutoff date for survival in E2100), 30 April 2009 (AVADO), and 23 February 2009 (RIBBON1).

The BV (Avastin) arm includes data from the Pac+BV arm of E2100, the Doc+BV arm of AVADO, and the T/Anth+BV and Cap+BV arms of RIBBON1.

The non-BV arm includes data from the Pac arm of E2100, the Doc+PL arm of AVADO, and the T/Anth+PL and Cap+PL arms of RIBBON1.

While AVADO and RIBBON1 confirm the activity of Avastin in MBC, they did not show the same magnitude of PFS improvement seen in E2100. Rather than invalidating E2100, the AVADO and RIBBON1 data indicate that the choice of chemotherapy partner is likely to influence the magnitude of PFS benefit seen with Avastin. These current data add to the learning about Avastin in MBC and reveal an unforeseen limitation in the ability of AVADO and RIBBON1 to confirm the findings of E2100, by illustrating the apparent magnitude of the differential impact of the chemotherapy partner paired with Avastin.

While multiple hypotheses can be generated for why a differential effect would be observed with distinct chemotherapy partners, the current lead hypothesis is that chemotherapies that provide for prolonged combined exposure with Avastin may yield the strongest treatment effects. In E2100, the combination with weekly paclitaxel allowed for prolonged exposure to both the cytotoxic and anti-angiogenic agents, as evidenced by a median chemotherapy duration of 7.3 months for Avastin plus paclitaxel, compared with a median chemotherapy duration of 5.1 months for paclitaxel alone. In contrast, treatment durations with combinations with docetaxel and anthracyclines are limited by the cumulative toxicities of the chemotherapy agents. Thus, the protocols for AVADO and RIBBON1 included limitations on exposure to docetaxel (maximum of nine 3-week cycles) and anthracyclines (maximum of eight 3-week cycles), corresponding to a maximum of only 27 or 24 weeks of combined treatment, respectively. In retrospect, these restrictions related to the tolerability of alternate chemotherapies represent limitations of their study designs in serving as confirmatory trials for E2100.

Although the differential effect observed in E2100, AVADO, and RIBBON1 is not well understood, the different magnitude of benefit observed in these studies (including differences within RIBBON1 for capecitabine compared with the other chemotherapies) establishes a real and credible hypothesis that warrant further investigation for a differential effect for Avastin with paclitaxel. Given the data, FDA goes too far in its Decision Memorandum when it dismisses the hypothesis that paclitaxel is a preferred partner with Avastin because the rationale for a "unique interaction between Avastin and paclitaxel … has not been substantiated."[61] Genentech should not be required to have *proven* that paclitaxel is a preferred chemotherapy partner in order to maintain accelerated approval; rather, Genentech should have the opportunity to conduct a further study while accelerated approval is maintained. Moreover, FDA's rejection of the possibility that there is a genuine differential effect with Avastin and paclitaxel in MBC is at odds with the Agency's prior advice in connection with discussions around the design of RIBBON1—that Genentech should consider separate studies with the different individual chemotherapy agents.[62]

[61] Decision Memorandum at 5.

[62] Minutes, 10 January 2006 Type B Meeting at 2.

FDA acknowledged that different chemotherapy backbones could modulate the magnitude of PFS benefit at a 10 January 2006 Type B meeting: "FDA understands that the treatment effect will vary according to the chemotherapy regimen used."[63] Genentech acknowledges FDA's position regarding the importance of the chemotherapy partner and, further, recognizes that AVADO and RIBBON1 were limited in their ability to serve as confirmatory trials for E2100.

FDA's approach to Avastin for MBC underscores the Agency's recognition that the chemotherapy partner may have an impact on the efficacy of Avastin. With knowledge of the AVADO final PFS data showing a lesser magnitude of median PFS effect (albeit with a trend for OS in the 15 mg/kg Avastin arm that subsequently eroded to no detrimental effect on OS),[64] Genentech requested and FDA granted accelerated approval limited to the combination of Avastin with paclitaxel, rather than granting a broad taxane-based label. FDA then articulated an approval standard for expansion of the label to include additional chemotherapies that was *specific* to the chemotherapy partner type: "[T]he treatment effect must be efficacious for the combinations of Bevacizumab and chemotherapy used."[65]

FDA thus anticipated the potential for variation in the size of the effect that would be seen with different chemotherapy agents. The Agency's decision now—that positive data involving other chemotherapy partners invalidates the data with paclitaxel based on demonstration of a significant but lesser magnitude of effect—is at odds with its prior actions and statements.

C. THE SAFETY PROFILE OF AVASTIN SUPPORTS AVASTIN'S REMAINING A TREATMENT OPTION IN MBC.

FDA states in its Decision Memorandum that its withdrawal proposal is based in part on the "substantial adverse reactions" and "substantial increases in toxicities" it sees

[63] Minutes, 10 January 2006 Type B Meeting at 2.

[64] The final PFS data showed an improvement in median PFS of 0.7–0.8 months, with hazard ratio of 0.64 (95% CI: 0.50, 0.82) for the 15 mg/kg arm. On the basis of interim OS data, the hazard ratio for OS was 0.65 (95% CI: 0.42, 1.02). *See* Appendix B.

[65] Minutes, 10 January 2006 Type B Meeting at 2.

with Avastin in breast cancer trials.[66] As reflected in such phrases, FDA has overstated the risk profile of Avastin in MBC.

Avastin's safety profile is well characterized and well known to oncologists. The more common adverse events associated with Avastin are clinically manageable such that treatment can be continued, and the more serious adverse events are infrequent yet still well described. The safety profile of Avastin in MBC was not changed by AVADO and RIBBON1, but rather was better defined by these studies. AVADO was particularly helpful in this regard, because it collected full safety profiles for all treatment arms, unlike E2100, in which use of the NCI's Adverse Event Expedited Reporting System was mandatory for the Avastin arm but not for the control arm.

Moreover, Avastin's safety profile as an anti-angiogenic biologic is distinct from the safety profile of cytotoxic chemotherapy agents, and the non-overlapping toxicities present potential advantages when Avastin is considered as additive therapy to paclitaxel. When Avastin is added to chemotherapy, there are of course incremental toxicities presented along with the incremental benefits. However, there is no basis to conclude that the additional toxicity or benefit–risk balance associated with Avastin is more severe or concerning than the additional toxicity or benefit–risk balance presented by other agents when they are added to chemotherapy. For example, E2100 and AVADO demonstrated no detriment to quality of life compared with chemotherapy alone, as measured by a standardized instrument (the Functional Assessment of Cancer Therapy–Breast or "FACT-B"), providing support for the tolerability of Avastin.[67] Avastin's safety profile is well described in its package insert and supports informed decisions by physicians and patients when they consider Avastin versus other medications in first-line MBC.

1. Avastin's Safety Profile Is Well Characterized.

The safety profile of Avastin for the treatment of breast cancer has been documented over the past decade within the Genentech Investigation New Drug ("IND") application. The safety information gathered to date (from the IND and postmarketing setting) is extensive. The safety information provided in support of

[66] Decision Memorandum at 4, 9.

[67] ISE, in-text Table 34 at 123.

Avastin's use for first-line MBC encompassed over 2400 patients—more patients than are studied in a typical oncology NDA or BLA submission. While conducting these development studies, Genentech duly submitted extensive annual reports to FDA that summarized safety information for the breast cancer program.[68] Through its oversight of the IND and its review of annual safety reports, FDA assessed emerging safety data and had multiple opportunities to comment or express concerns if the Agency found that the safety profile associated with the Avastin breast cancer program was in excess of what was expected or appropriate. FDA did not raise such comments or concerns.

The resulting safety profile of Avastin is well understood and clearly documented in the Avastin® Package Insert. The package insert reflects real-world data from more than 800,000 patients who have received Avastin,[69] including MBC patients who have received Avastin largely in combination with paclitaxel.

In addition, Genentech continuously engages in assessments of the safety profile of Avastin. For example, Genentech's parent company (F. Hoffmann–La Roche) sponsored ATHENA (described above in Section II.A.2) in the postmarketing setting to assess further the safety profile of Avastin in MBC.[70] ATHENA confirmed the well-characterized safety profile of Avastin in MBC, uncovering no new safety signals.

The adverse events typically associated with Avastin include hypertension and proteinuria, which together account for the majority of the increase in reporting of Grade ≥3 adverse events when compared with chemotherapy alone. The more common all-grade adverse events associated with Avastin—including hypertension and proteinuria—are often asymptomatic for patients and are manageable with clinical interventions consistent with clinical practice.

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[68] These reports included, but were not limited to, narrative or tabular safety summaries, by body system, of the most frequent and most serious adverse events; a list of all patient deaths with cause of death; a list of all patient dropouts in association with adverse experiences, whether or not they are thought to be related to the investigational product; a summary of all IND safety reports submitted during the previous year; and a summary of significant foreign marketing developments.

[69] *See* Appendix D.

[70] Smith IE, et al. Ann Oncol Advance Access. Epub 5 September 2010.

For example, most cases of hypertension—which is a diagnosis internists commonly manage—can be controlled adequately using standard antihypertensive treatment. Blood pressure levels typically decrease after cessation of Avastin, and treatment-induced hypertension very rarely leads to discontinuation of Avastin or serious or lasting sequelae. Urinary protein is monitored with dipstick urinalysis testing during Avastin treatment, and the presence of proteinuria is managed with an algorithm based on the urinalysis results. Similar to hypertension, proteinuria is generally reversible when Avastin is discontinued, and it has not been associated with renal impairment. Essentially all chemotherapy drugs have toxicities that oncologists (who are trained as internists) regularly manage, such as nausea, neutropenia, left ventricular dysfunction, and neuropathy. Monitoring for hypertension and proteinuria are similarly manageable for an experienced clinician.[71]

More severe adverse events associated with Avastin include gastrointestinal perforation, arterial thromboembolic events, venous thromboembolic events, higher-grade bleeding, congestive heart failure, and reversible posterior leukoencephalopathy syndrome ("RPLS"). These events are serious, but their incidence is low. These adverse events are well documented in the Avastin® Package Insert, which appropriately identifies the most serious risks in a boxed warning and then documents remaining risks in the "Warnings and Precautions" and "Adverse Reactions" sections of the insert.[72] By identifying both the most serious but less common risks,[73] and the more common but manageable risks, the package insert allows physicians and patients to make informed decisions about the benefit–risk profile of Avastin.

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[71] As Dr. Pazdur has acknowledged: "We definitely have a much different paradigm in oncology than in any other therapeutic area. …All of our drugs are used by medical oncologists with specialized training. We have basically mechanisms in place to monitor these toxicities; we have investigators as well as nursing staffs that are quite familiar with drug safety issues." Michael McCaughan, Carving REMS out of Oncology? FDA, ASCO Plan Follow-Up Workshop, The RPM Report, 1 November 2010.

[72] Avastin® (bevacizumab) Package Insert, Genentech, Inc., *available at* http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf (last visited 14 January 2011).

[73] For example, the boxed warning refers to gastrointestinal perforations occurring in up to 2.4% of patients, advises physicians how to avoid surgery and wound-healing complications, and warns of increases in severe or fatal hemorrhage.

2. AVADO and RIBBON1 Did Not Change Avastin's Safety Profile.

As FDA recognized, AVADO and RIBBON1 did not change the well-established safety profile of Avastin.[74] Individually, the studies revealed no new safety signals. The same was true when the AVADO and RIBBON1 safety data were pooled with the E2100 data.

In addition, in all three of these studies, the median duration of chemotherapy was longer in Avastin-treated patients than in control patients (with the exception of taxane-treated patients in RIBBON1, who had a similar duration of chemotherapy treatment).[75] This indicates that the addition of Avastin did not compromise the delivery of chemotherapy, as well as providing more opportunity for recording of adverse events on the Avastin arm.

3. Avastin Does Not Present Greater Overall Safety Concerns than Other Therapeutic Options.

All chemotherapeutics are associated with serious risks. Placing the assessment in context of the indication and patient population that is likely to be treated is central to the overall assessment of risk and potential benefit. Avastin's risk profile is distinct from that of well-accepted first-line treatments for MBC, but the overall degree of risk is comparable to that of other agents that are added to chemotherapy; and for some patients, Avastin's distinct safety profile may be more favorable relative to that of other therapies.

It is instructive to evaluate the risk profile for Gemzar®, which is approved in first-line MBC in combination with paclitaxel. The risks of Gemzar® are highlighted directly for patients in the Patient Therapy Guide.[76] This Guide acknowledges the need for patient awareness of the high incidence of side effects associated with Gemzar® use, such as neutropenia (experienced by 7 of 10 patients), anemia (7 of 10), low platelet count (1 of 4), alopecia (9 of 10), neuropathy (2 of 3), and joint and muscle pain (3 of 10), as well as the necessity for careful monitoring, including monitoring of

[74] FDA, Briefing Book, 20 July 2010 ODAC at 25 ("Overall, the incidence of AEs is not significantly different than currently described in the Avastin package insert.").

[75] Genentech, Inc., Briefing Book, 20 July 2010 ODAC at 50.

[76] Gemzar® Patient Therapy Guide, Eli Lilly and Company, *available at* http://www.gemzar.com/Documents/pdf/MBCTherapyGuide.pdf (last visited 14 January 2011).

liver and kidney function.[77] The Gemzar® labeling also warns of severe and uncommon toxicities, including pulmonary toxicity such as adult respiratory distress syndrome, hemolytic uremic syndrome, and/or renal failure leading to death or requiring dialysis, severe and/or fatal hepatotoxicity, peripheral vasculitis and gangrene, congestive heart failure, severe skin toxicity, and toxicity related to infusion time and dosing frequency. The labeling also emphasizes the importance of monitoring for dose-limiting myelosuppression, renal function, and liver function.

The differential risk profile of Gemzar® is reflected in real-world clinical practice. Gemzar® is not commonly used in first-line MBC in combination with paclitaxel, and its use has been much more limited than that of Avastin,[78] likely owing to clinical experience in the safety and efficacy profiles of the two medications.

More generally, no single regimen has emerged as a standard of care that is appropriate for all patients. Clinicians value having multiple options for patients and recommend a specific therapy on the basis of factors such as disease features, patient characteristics, prior treatment history, and patient preferences. When selecting drugs for combination therapy, it is desirable to have non-overlapping toxicity profiles in order to produce additive antitumor effects without enhancing chemotherapy-related toxicity. Combination therapies, such as chemotherapy doublets, are particularly indicated in the first-line MBC setting when a rapid response is required (e.g., bulky disease, impending end organ compromise).[79]

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[77] Gemzar® Patient Therapy Guide at 8–13.

[78] 2010 ASCO Annual Meeting, Breast Cancer Track, Controversies in the Management of Metastatic Breast Cancer Education Session. Clifford Hudis, M.D., Chair and Speaker (noting that although the pivotal study for Gemzar® in combination with paclitaxel demonstrated an OS benefit, the regimen has had limited uptake likely as the result of toxicity and other factors, including that the Gemzar® study participants were not pretreated with taxanes, whereas currently many patients have been pretreated with taxanes).

According to available market data, prior to Avastin's approval in MBC the combination of Gemzar® + paclitaxel accounted for a maximum of 4% of the total first-line HER2-negative prescriptions in 2006 and 2007. However, after Avastin's approval, the Gemzar® + paclitaxel combination's proportion of new prescriptions dropped to less than 1% in 2009–10. In contrast, the proportion of new prescriptions for Avastin + paclitaxel in 2009–2010 was 19%–26%, and Avastin's total percentage of new prescriptions was 53%–59%, dropping to a currently estimated 43% and 35% (±5%) in the third and fourth quarters of 2010 after the 20 July 2010 ODAC meeting. *See* Appendix E.

[79] Beslija S, et al. Ann Oncol 2009.

Unlike chemotherapy doublets, Avastin (an anti-angiogenic biologic) and paclitaxel (a mitotic inhibitor chemotherapy) have non-overlapping toxicity profiles. For example, the more common Grade 3 and 4 toxicities with paclitaxel are granulocytopenia, sensory neuropathy, and fatigue,[80] whereas the more frequently observed adverse events associated with Avastin are hypertension and proteinuria. As a result, the addition of Avastin to paclitaxel results in a safety profile that is different from that observed with a chemotherapy doublet. Indeed, Avastin plus paclitaxel is often chosen by clinicians over other available combinations on the basis of an individual patient's clinical circumstances and preferences, including the safety profile that is appropriate for the patient.

In practice, when patients and clinicians are considering whether to add another agent to the selected chemotherapy backbone, one of the key factors they will assess is the incremental toxicity that may occur beyond the toxicities associated with the chemotherapy backbone alone, balanced with the expected increase in efficacy. For patients for whom paclitaxel is the appropriate chemotherapy backbone, the data suggest that the incremental toxicity and risks associated with the addition of Avastin are similarly acceptable to, if not more favorable than, those associated with other chemotherapy options.

4. FDA Has Not Fairly Characterized the Safety Profile of Avastin.

FDA has overstated the incidence and severity of adverse events associated with Avastin in several respects. The statements of FDA at the 20 July 2010 ODAC meeting[81] attribute toxicities such as gastrointestinal perforation ("holes in the intestine") to Avastin without acknowledging the low incidence in patients treated both with chemotherapy alone and with chemotherapy plus Avastin. In the pooled safety data from E2100, AVADO, and RIBBON1, the incidence of the toxicities noted by FDA include gastrointestinal perforation (0.3% for chemotherapy, 0.5% for chemotherapy plus Avastin), bleeding (0.4% for chemotherapy, 1.6% for

[80] Taxol® (paclitaxel) Package Insert, Bristol-Myers Squibb, *available at* http://packageinserts.bms.com/pi/pi_taxol.pdf (last visited 14 January 2011).

[81] FDA, Briefing Book, 20 July 2010 ODAC at 16 ("Other clinically significant events attributable to bevacizumab that were reported in [AVADO] were wound healing complications, fistula, gastrointestinal perforation and proteinuria."); FDA, Slides, 20 July 2010 ODAC at 71 ("Toxicities attributed to bevacizumab: hypertension, bleeding/hemorrhage, gastrointestinal perforation/fistulas, arterial and venous thromboembolic events, and wound healing complications.").

chemotherapy plus Avastin), venous thromboembolism (3.8% for chemotherapy, 3% for chemotherapy plus Avastin), arterial thromboembolism (0.3% for chemotherapy, 1.9% for chemotherapy plus Avastin), and fistula (0.3% for chemotherapy and 0.4% for chemotherapy plus Avastin). These facts indicate that the selected adverse events are seen with chemotherapies used in MBC with or without Avastin, the incidence is low in both pooled treatment groups, and the absolute increase in Avastin-treated patients for these adverse effects is small.

In the NOOH, FDA noted that Avastin led to an "overall increase in serious adverse events, grade 3 through 5 adverse events (serious or life-threatening events or death), and adverse events related to bevacizumab."[82] FDA made similar statements in the Decision Memorandum accompanying the NOOH.[83] These statements do not acknowledge that all therapies in first-line MBC lead to an overall increase in adverse events. These statements also do not reference important facts about the increases in adverse events for Avastin, including that (i) the majority of Grade 3–5 adverse events were reported as Grade 3, (ii) the increase in adverse events observed in these studies is consistent with that observed with the use of Avastin across a range of cancers, and (iii) much of the increase in adverse events is driven by higher incidences of hypertension and proteinuria, both of which are often asymptomatic and manageable with clinical interventions consistent with clinical practice. Furthermore, the grading of hypertension changed during the course of the Avastin studies in MBC. Some Grade 3 hypertension in E2100, for instance, is considered to be Grade 2 in the current common toxicity grading schema.

Likewise, FDA has not placed treatment-related deaths in the proper context. In the Decision Memorandum, FDA noted that "deaths attributed to Avastin ranged between 0.8 to 1.2%,"[84] but declined to point out that the pooled safety data show that treatment with Avastin in combination with chemotherapy did not cause an increase in treatment-related death compared with chemotherapy alone. The incidence of death

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[82] NOOH at 3.

[83] Decision Memorandum at 4 ("Addition of Avastin to standard chemotherapy regimens resulted in an overall increase in serious adverse events, grade 3 through 5 adverse events, and adverse events related to Avastin."); Decision Memorandum at 6 (noting "a marked increase in clinically serious, life-threatening and disabling adverse events and therapy-related deaths").

[84] Decision Memorandum at 6.

due to adverse event or protocol therapy was *identical* in the 982 chemotherapy-treated patients, 1.8%, and the 1427 chemotherapy plus Avastin–treated patients, 1.8%, in the pooled analysis of E2100, AVADO, and RIBBON1.[85] More generally, FDA's practice of citing adverse events associated with Avastin without any discussion of their incidence, or without acknowledging that these same adverse events are seen with chemotherapy alone, creates a misleading impression of heightened, unmanageable risk. In the Decision Memorandum, for example, FDA stated

> Avastin-related toxicities include hypertension, bleeding/hemorrhage, wound healing complications including wound dehiscence, perforation and fistula/abscess formation. Other Avastin-related toxicities include arterial thromboembolic events (stroke, myocardial infarction), venous embolic events, febrile neutropenia, left ventricular dysfunction, and reversible posterior leukoencephalopathy.[86]

In fact, as described above, most of the more severe adverse events occur at a low frequency.[87]

Similarly, in a public call following the NOOH, FDA singled out a report of a gastrointestinal perforation in an 84-year-old woman to illustrate the potential risks of Avastin and "the sudden onset and severity of these toxicities."[88] FDA did not note

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[85] Genentech, Inc., Slides, 20 July 2010 ODAC at CC-11. Clinicians also question FDA's focus on deaths associated with Avastin. As noted by Dr. Adam Brufsky of the University of Pittsburgh Cancer Institute, "The FDA already has an ODAC vote … [ODAC] seem[s] to have been focused on the death rate in the Avastin-containing arm, which seems to be the ODAC justification to vote to remove the indication. But those of us who are familiar with the published data have a hard time understanding from where they derived an increased death rate. The bottom line is you have a drug that was approved based on PFS … Several confirmatory studies show that Avastin results in increased PFS without any substantial increase in toxicity beyond what already has been found." Avastin Controversy Shakes Up Oncology Community, Clinical Oncology News, October 2010:5:10.

[86] See, e.g., Decision Memorandum at 4; Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Breast Cancer Community (16 December 2010) at 2, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237286.pdf (last visited 14 January 2011) ("Side effects observed included kidney damage, development of holes in parts of the body (for example, nose, stomach, intestines), massive bleeding requiring blood transfusions, and various cardiovascular problems (for example heart attack, stroke, clotting in arteries, chest pain and reduced blood flow to the brain).")

[87] Genentech, Inc., Briefing Book, 20 July 2010 ODAC at 53.

[88] Transcript, FDA call with stakeholders (16 December 2010) ("There are several reports which serve to better illustrate the potential risks than these raw numbers, and I will summarized one of

that Avastin is associated with a 0.5% incidence of gastrointestinal perforation compared with a 0.3% incidence in the chemotherapy-only patients in the pooled safety analysis.[89] Likewise, FDA focused on the development of RPLS as a serious side effect of Avastin use;[90] however, only a single case of RPLS was observed among 1427 patients enrolled in E2100, AVADO, and RIBBON1—an incidence of 0.07%.[91] Singling out a rare, serious, and reversible side effect such as RPLS gives the false impression of a higher incidence of such an event than is warranted by the data.

D. INDEPENDENT SCIENTIFIC DECISION-MAKERS HAVE REAFFIRMED THE VALUE OF AVASTIN IN COMBINATION WITH PACLITAXEL.

1. The European Medicines Agency Has Recommended the Continued Authorization of Avastin in Combination with Paclitaxel.

The CHMP of the EMA reviewed the same data for Avastin in MBC that were reviewed by FDA and concluded that "the benefits of Avastin in combination with paclitaxel outweigh its risks and that this combination remains a valuable treatment option for patients suffering from metastatic breast cancer."[92] In the questions and answers accompanying this recommendation, CHMP indicated that the AVADO and RIBBON1 data supported its assessment of the benefit–risk of Avastin in

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those. This is a report of an 84-year-old woman with metastatic breast cancer, who after three doses of Avastin and paclitaxel, was admitted with abdominal pain. She was diagnosed with perforation of her colon. There was no evidence of the tumor at that site. She was hospitalized but died a week later as a result of sepsis. The sudden onset and severity of these toxicities are very important in the consideration of the risk–benefit profile that FDA utilized in coming to this decision with the proposal for removal of the indication for breast cancer.").

[89] Genentech, Inc., Slides, 20 July 2010 ODAC at CC-9.

[90] Transcript, FDA Media Briefing on Avastin (16 December 2010), *available at* http://www.fda.gov/NewsEvents/Newsroom/MediaTranscripts/ucm198091.htm at 6 (last visited 14 January 2011) ("And the development of a neurologic condition called reversible posterior leukoencephalopathy syndrome, or RPLS, characterized by high blood pressure, headaches, confusion, seizures, vision loss resulting from swelling of the brain have all been observed in patients treated with Avastin.").

[91] Integrated Summary of Safety ("ISS"), in-text Table 11 at 16.

[92] Press Release, European Medicines Agency, European Medicines Agency Completes Its Review of Avastin Used in Breast Cancer (16 December 2010), *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/12/news_detail_001166.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1 (last visited 14 January 2011).

combination with paclitaxel. Specifically, CHMP stated: "For paclitaxel, … Avastin has been *convincingly* shown to prolong progression-free survival without a negative effect on overall survival, and *the new study data support this conclusion*. Therefore, the Committee concluded that the benefit–risk balance for this combination treatment remains positive."[93]

The difference in the conclusions reached by FDA and CHMP is striking. CHMP has recommended retaining marketing authorization (without conditions) for Avastin plus paclitaxel. FDA has proposed withdrawal of the MBC indication, rather than alternative approaches such as maintaining accelerated approval with labeling restricted to use with weekly paclitaxel and a requirement to conduct a confirmatory study of Avastin plus paclitaxel.

2. <u>Avastin Continues to Be Endorsed in Influential Consensus Treatment Guidelines and by Leading Clinicians.</u>

In October 2010, the NCCN affirmed its recommendation for use of Avastin in combination with paclitaxel, after having reviewed the same data that were considered by the 20 July 2010 ODAC.[94] The NCCN Guidelines are developed and updated on the basis of an evidence-based process, with explicit review of scientific evidence by multidisciplinary panels of expert physicians.

The contrasting conclusions of ODAC and the NCCN may stem from the differing composition of these groups and their distinct directives. ODAC is a heterogeneous panel of advisors consisting of oncologists with different specialty expertise, statisticians and consumer and patient advocates. ODAC is asked to advise FDA on a broad spectrum of oncologic drugs across the spectrum of cancer treatment, which is increasingly specialized. Only two of the 13 ODAC members at the 20 July 2010 ODAC meeting were breast cancer oncologists (one breast oncologist and one women's cancer specialist), and both were temporary voting members recalled from

[93] European Medicines Agency, Questions and Answers on the Review of Avastin (bevacizumab) in the Treatment of Metastatic Breast Cancer (16 December 2010) (emphasis added).

[94] Press Release, NCCN, NCCN Guidelines for Breast Cancer Updated; Bevacizumab Recommendation Affirmed (19 October 2010), *available at* http://www.nccn.com/news/764-nccn-guidelines-for-breast-cancer-updated-bevacizumab-recommendation-affirmed.html (last visited 14 January 2011).

the 2007 ODAC meeting on E2100 by FDA.[95] A key component of the evaluation of Avastin as a treatment option is understanding how patients and physicians can weigh the safety information as part of their benefit–risk assessment for Avastin in MBC. Hence, a richer perspective of clinicians on ODAC familiar with the use of Avastin in the clinic would have been valuable to inform discussion of the use of Avastin in MBC.

By contrast, the NCCN Breast Cancer panel comprises clinicians and oncology researchers specializing exclusively in breast cancer from the NCCN Member Institutions. Thus, the continued inclusion of Avastin with paclitaxel in the NCCN Guidelines reflects the recommendations of breast cancer clinicians focusing on treatment experiences and clinical realities, whereas ODAC's recommendation reflects the views of a heterogeneous advisory panel including a more generalist group of oncologists, statisticians, and others evaluating a body of clinical study data as presented by FDA and the sponsor. Individuals with both expertise in breast oncology and experience with the clinical use of Avastin are best positioned to evaluate the benefit–risk balance of Avastin in MBC. Respectfully, we submit these qualities are more clearly reflected in the composition of the NCCN Breast Cancer Guidelines panel than in ODAC.

Consistent with the NCCN's recommendation, clinicians support the continued approval of Avastin for use in MBC.[96] For example, Dr. Kathy S. Albain, Professor of

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[95] Aman Buzdar, M.D., Professor of Medicine, Department of Breast Medical Oncology, University of Texas, M.D. Anderson Cancer Center and Joanne Mortimer, M.D., Director Women's Cancers Program, Vice Chair Medical Oncology, Associate Director for Affiliate Programs, Professor, Division of Medical Oncology, Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center. The oncologist ODAC voting members were: Chair Wyndham Wilson, M.D., Ph.D., Chief Lymphoma Therapeutics Section, Center for Cancer Research, National Cancer Institute (specializing in lymphoma); Ralph Freedman, M.D., Ph.D, Clinical Professor, Department of Gynecologic Oncology, University of Texas, M.D. Anderson Cancer Center; Jean Grem, M.D., F.A.C.P., Professor of Medicine, Department of Internal Medicine, Section of Hematology/Oncology, University of Nebraska Medical Center (specializing in gastrointestinal malignancies); Patrick Loehrer, Sr., M.D., Director, Melvin and Bren Simon Cancer Center, Indiana University (specializing in testis cancer, gastrointestinal cancer and thymoma); Mikkael Sekeres, M.D., M.S., Associate Professor of Medicine, Department of Hematologic Oncology and Blood Disorders, Taussig Cancer Institute, Cleveland Clinic (specializing in leukemia). In addition, Dr. Gary Lyman, Professor of Medicine, Director, Comparative Effectiveness and Outcomes Research, Duke Comprehensive Cancer Center and Duke University was a temporary voting member.

[96] Furthermore, although FDA's actions put this in jeopardy, certain private payers continue to provide coverage for Avastin in first-line MBC, based on the NCCN guidelines, and continue to consider

Medicine and Director, Breast Research Program, Loyola University Chicago Stritch School of Medicine, stated, "If the FDA removes the current label, we may be throwing the baby out with the bathwater … It would be disappointing [ ] to lose this agent from our armamentarium."[97] Dr. Joyce O'Shaughnessy of Baylor Sammons Cancer Center, and Co-Chair, Breast Cancer Research, US Oncology, explained:

> I do not think Avastin should lose its breast cancer indication. Weekly Taxol/Avastin is one of the few effective therapies we have for metastatic triple-negative breast cancer and for other aggressive cancers that have had a short disease-free interval following adjuvant chemotherapy. Metastatic triple-negative breast cancer is a virulent, often drug-resistant and symptomatic cancer and not having Avastin to offer these patients would take away one of the few effective options we have for them. E2100 was highly positive. AVADO and RIBBON-1 are both positive. Avastin is a safe agent and is associated with a very low, less than 1% chance of treatment-related death, no different from the chemotherapy-alone arms of the studies. These facts justify Avastin remaining as a choice in the treatment of virulent metastatic breast cancer.[98]

Similarly, John Finnie, MD, Staff Hematologist and Medical Oncologist at St. John's Mercy Medical Center, has stated:

> I would favor maintaining the indication for this targeted therapy for my breast cancer patients, based not only on its safety data but also [on its] consistently seen improved outcomes, on a par with other approved agents in the metastatic setting. The decision by ODAC to consider withdrawing the FDA approval of bevacizumab is based on the lower relative benefit in subsequent studies; however, nearly all medical oncologists could cite examples of

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Avastin an important option for first-line MBC patients. WellPoint Inc. spokesperson Lori McLaughlin indicated that the company considers Avastin medically necessary for first-line treatment of metastatic breast cancer that is HER2 negative. Susan Schaeffer & Stephen Hansen, Label: no; Access: yes, BioCentury v. 18 n. 54, A1, A4 (20 December 2010).

[97] "Bevacizumab in Advanced Breast Cancer: FDA Committee Ruling Sparks Response from Oncology Community; Nine Members of the Oncology Community Speak out about Bevacizumab's Role in Metastatic Breast Cancer, The ASCO Post, September 2010, *available at* http://www.ascopost.com/articles/september-2010/nine-members-of-the-oncology-community-speak-out--about-bevacizumab%E2%80%99s-role-in-metastatic-breast-cancer (last visited 14 January 2011).

[98] Avastin Controversy Shakes Up Oncology Community, Clinical Oncology News, October 2010.

patients treated with this agent, showing clinical benefit with very good tolerability.[99]

This strong scientific support for the continued use of Avastin for the treatment of first-line MBC, particularly in combination with paclitaxel, underscores that the data still establish the potential benefit of the drug and the need to retain Avastin as an approved therapeutic option to be used where deemed appropriate by physicians and patients.

3. Continuing Utilization Indicates That Clinicians Believe Avastin Has a Favorable Benefit–Risk Profile in MBC.

Following the 20 July 2010 ODAC meeting and the ensuing uncertainty about the regulatory status of Avastin's indication for MBC, the use of Avastin has decreased, but there remains a substantial level of persistent use. Specifically, Avastin's proportion of new prescriptions has decreased from 59% prior to the ODAC decision to 35% (±5%) in the fourth quarter of 2010 based on current estimates.[100] This trajectory shows that clinicians and patients have modified their treatment choices based on the uncertainty surrounding the ODAC decision and FDA actions, but despite this uncertainty (and an agreed-upon marketing moratorium), a substantial core level of use continues.

This use pattern indicates that clinicians and patients continue to view Avastin as an important option for certain patients and, in particular, are not finding that the drug has an unacceptable toxicity profile. This emerging utilization pattern indicates that physicians and patients can make informed treatment choices for individual circumstances and that FDA should not take a broad-based regulatory action that removes Avastin as an available option in the armamentarium.

III. FDA IS SETTING A NEW APPROVAL STANDARD FOR FIRST-LINE MBC THAT COULD DETER DRUG DEVELOPMENT.

FDA's proposal to withdraw the approval of Avastin for MBC is based on a new standard for the efficacy showing that a therapy must make in first-line MBC. The Agency previously—and appropriately—followed a more flexible approach based on data showing a medicine's effect on PFS or other disease progression endpoints,

[99] Avastin Controversy Shakes Up Oncology Community, Clinical Oncology News, October 2010.

[100] *See* Appendix E.

together with data on OS. Now FDA has stated that improvement in PFS is not adequate unless it is of a large (but unspecified) magnitude (such as the substantial 5.5-month improvement observed in E2100) and that otherwise there must be an improvement in OS to support approval.

FDA's newly articulated standard carries potential risks for the future availability of medications for the first-line treatment of patients with MBC. No other drug has shown a magnitude of effect on median PFS as large as seen for Avastin with weekly paclitaxel in E2100. At the same time, there are substantial scientific obstacles to the detection of statistically significant improvements in OS in the first-line MBC setting. Existing drugs for first-line MBC currently on the market were not approved on the basis of such a standard, and few drugs for first-line MBC in the future will be able to make such a showing.

The risks to innovation from the standard FDA is now imposing are further exacerbated by the lack of clarity in FDA's current approach. Genentech recognizes the need for a certain degree of case-by-case evaluation based on the particular circumstances presented by a given compound and dataset. However, FDA is requiring a large magnitude of improvement in PFS without any statement of what particular magnitude must be shown. FDA is also imposing this requirement without having presented a proposed framework for feedback to the broader stakeholder community.[101] The Agency is applying this new standard to Avastin without having communicated it in a transparent manner to Genentech during the discussions that outlined the conditions for converting from accelerated to full approval in MBC.

A. PRIOR FDA APPROVALS IN MBC DO NOT MEET THE STANDARD FDA IS USING FOR AVASTIN.

FDA has accepted disease progression endpoints—such as PFS and TTP—as the basis of regulatory approvals in MBC without requiring a specific or large magnitude of effect as large as that observed in E2100 or a demonstration of OS benefit. Table 7 identifies FDA-approved agents in MBC, the endpoint supporting approval, and the magnitude of effect shown.

[101] Notably, FDA recently announced that it will be convening ODAC on 8 February 2011 to discuss ways to improve postmarketing trials required to confirm the benefit of drugs that received accelerated approval. 76 Fed. Reg. 1181 (7 January 2011). This meeting and discussion obviously comes *after* FDA has acted on the postmarketing trials for Avastin in MBC.

Table 7
FDA-Approved Agents in MBC, 1996–2010 [102]

Drug, Date Approved	Approval Type	Endpoints	Improvement in Median PFS/TTP (months)
First-line therapy			
Herceptin®, 1998 [a]	Full	TTP, OS	2.7 [b] 4.2 [c]
Gemzar®, 2004 [d]	Full	TTP	2.3
Avastin, 2008	Accelerated	PFS	5.5
Second-line therapy			
Taxol®, 1994	Full	TTP	1.2 [e]
Taxotere®, 1996	Accelerated	RR	NR
Taxotere®, 1998	Full	RR, TTP, OS	1.8
Abraxane®, 2005	Full	RR	1.3 [f]
Tykerb®, 2007	Full	TTP/PFS	2.1 [g] 1.4 [h]
Ixempra®, 2007	Full	PFS, RR	1.7
Third-line therapy			
Halaven™, 2010	Full	OS	1.4

IRC = independent review committee; OS = overall survival; NR = not reported; PFS = progression-free survival; RR = response rate; TTP = time to disease progression.

[a] Supported by significant improvement in 1-year survival; there was a trend in OS that did not meet statistical significance at the time of approval.

[b] For the combination of Herceptin® with chemotherapy (anthracycline/cyclophosphamide or paclitaxel).

[c] For the combination of Herceptin® with paclitaxel.

[d] Supported by a trend in OS from an interim analysis; this was non-significant in two sensitivity analyses performed by the FDA statistical reviewer.

[e] Comparison of low-dose and high-dose arms.

[f] Per investigator data. IRC assessment indicates a 0.3-month difference. Information was not included in the Abraxane® Package Insert, as FDA did not consider the TTP data to be sufficiently mature or robust for analysis.

[g] As assessed by the IRC.

[h] As assessed by investigators.

Specifically in the first-line MBC setting, drugs have received full approval on the basis of an effect on disease progression well below that seen in E2100 with no established statistically significant improvement in OS.

[102] Package Inserts at time of approval, which are available at Drugs@FDA.

FDA has repeatedly drawn a distinction between the efficacy data for Avastin and the data that underpinned approval of Gemzar® and Herceptin® (trastuzumab), citing Gemzar® and Herceptin® as examples of recent approvals in first-line MBC that were purportedly supported by both OS and PFS improvements. FDA made this assertion at the July 2010 ODAC meeting that considered E2100,[103] and FDA repeats it in the Decision Memorandum.[104] The data do not support this distinction. Gemzar® in particular does not meet the criteria that FDA is now setting forth—i.e., a large magnitude of PFS benefit and/or a *statistically significant* benefit in OS. Herceptin® was approved on the basis of a TTP benefit (4.2 months with paclitaxel) larger than that of Gemzar®, but approval was not supported by a statistically significant improvement in OS at the time of its approval, and in any event is in the distinct HER2-positive patient population.[105]

Table 8 presents the efficacy results from the pivotal studies supporting the initial approvals of Avastin and Gemzar®.

[103] FDA, Slides, 20 July 2010 ODAC at 6 (noting Herceptin® and Gemzar® received regular approval in first-line MBC based on overall survival and Avastin received accelerated approval in first-line MBC based on PFS); Transcript, 20 July 2010 ODAC at 65 (statement of Dr. Pai-Scherf) ("Trastuzumab plus chemotherapy and gemcitabine plus paclitaxel received regular approval based on the statistically significant improvement in overall survival compared with the control arms.")

[104] Decision Memorandum at 4.

[105] Herceptin® was approved in 1998 on the basis of a 4.2-month effect on median TTP in combination with paclitaxel (2.7 months overall), improvement in the 1-year survival rate (11% improvement, $p < 0.01$), and an OS trend that did not meet statistical significance ($p = 0.104$). Subsequent to the original approval, a statistically significant OS benefit was demonstrated. Herceptin® updated OS results: HR = 0.80 (95% CI: 0.64, 1.00); $p = 0.046$ (added to product label in a supplementary submission). Herceptin® Package Insert, Genentech, Inc., *available at* http://www.gene.com/gene/products/information/pdf/herceptin-prescribing.pdf (last visited 14 January 2011). *See also* Transcript, 20 July 2010 ODAC at 177 (statement of Dr. Cortazar) ("Herceptin was approved on the basis of a time-to-progression advantage. At that time we also had some preliminary data on the 12-month overall survival … So [ ] initially, [it] was time to progression, but preliminary data from survival which was confirmed later on.").

Table 8
Efficacy Results from the Pivotal Studies of Avastin and Gemzar®
Available to FDA at the Time of Approval

	Avastin (E2100) [a] (n=722)	Gemzar® [b] (n=529)
Study type	Open label	Open label
PFS/TTP	11.3 vs. 5.8 months Δ=5.5 months HR=0.48, p<0.001	5.2 vs. 2.9 months Δ=2.3 months HR=0.65, p<0.001
OS	HR=0.87 95% CI: (0.72, 1.05), p=0.14 481 deaths	HR=0.82 95% CI: (0.67, 1.0), p=0.049 [c] 377 deaths
One-year survival	Δ=7.4%, p=0.017	Δ=10.5%, p=0.012
Objective response rate	Δ=26.7%, p<0.001	Δ=18.7%, p<0.001

CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; TTP=time to disease progression.

[a] Avastin® 2008 Package Insert and ISE.

[b] Gemzar® Summary Basis of Approval.

[c] Two OS sensitivity analyses conducted by the FDA statistical reviewer had p>0.05, leading the reviewer to conclude that the interim survival data showed a "trend" in favor of the Gemzar® arm.

As shown in Table 8, when Gemzar® was approved in 2004, the OS data that were available at the time of approval were based on an interim analysis and the p-value associated with the hazard ratio (0.049) did not reach statistical significance for the interim review. More importantly, when the OS data matured, the effect on OS continued to be not statistically significant.[106] Thus, the same conclusion must be drawn from the OS data supporting the current Gemzar® approval and the OS data from E2100—i.e., the hazard ratios favor the test arm, but the effects on OS are not statistically significant.

The divergence between the standard that FDA has articulated for Avastin and the standard that FDA applied to Gemzar® is especially striking because FDA granted full approval to this other therapy. FDA now proposes to withdraw accelerated approval for Avastin, even though Avastin's use in first-line MBC is supported by data that are comparable to the data upon which FDA maintains a full approval for

[106] Gemzar® (gemcitabine HCl) Package Insert, Eli Lilly and Company, *available at* http://pi.lilly.com/us/gemzar.pdf (last visited 14 January 2011). Gemzar® updated OS results at 440 deaths: HR=0.86 (95% CI: 0.71, 1.04); p=0.12. *Id.*

Gemzar®. This disparate treatment of Avastin underscores the risk to development presented by FDA's approach to Avastin, and this approach is contrary to FDA's regulations.[107] If the standard that FDA seeks to apply to Avastin were applied to Gemzar®, it arguably would not be approved today. Going forward, the standard may unduly limit future approvals in this area of significant unmet medical need.[108,109] The disparate treatment of Avastin and Gemzar® also fails a basic tenet of administrative law requiring an agency to treat like cases in a like manner.[110]

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[107] 57 Fed. Reg. 58942, 58942 (11 December 1992) (indicating that "the requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval."). *See also* 57 Fed. Reg. at 13236 (reiterating that "the requirements for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval").

[108] Clinicians have remarked on the inconsistency in FDA's approval standards. For example, Dr. Harold J. Burstein at Harvard Medical School noted, "There has not been a single metric by which the FDA has reviewed drugs for advanced breast cancer … we use lots of drugs that have not been shown to improve survival." *See* Bevacizumab in Advanced Breast Cancer: FDA Committee Ruling Sparks Response from Oncology Community; Nine Members of the Oncology Community Speak out about Bevacizumab's Role in Metastatic Breast Cancer, The ASCO Post, September 2010.

[109] RIBBON2 represents another example of FDA's acting inconsistently with the standards it has applied to prior approvals in MBC. In the second-line setting, RIBBON2 demonstrated efficacy results for Avastin that were stronger than (or at least, comparable to) the efficacy results from the pivotal study for Ixempra®, an approved second-line therapy; however, FDA determined that RIBBON2 did not demonstrate clinical benefit. RIBBON2 (which evaluated Avastin or placebo with investigator's choice of chemotherapy in women with MBC who had previously received chemotherapy as first-line treatment in the metastatic setting) showed a 2.1-month increase in median PFS with a 22% reduction in the risk of disease progression or death (HR = 0.78, p = 0.0072) and an increase in response rate of 9.9% (p = 0.0193). Brufsky A, Bondarenko IN, Smirnov V, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, Phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer [abstract]. SABCS 2009:abstract 42. FDA approved Ixempra® for second-line treatment of MBC in combination with capecitabine based on a smaller improvement in median PFS (1.6 months) and a 20.4% improvement in response rate. Ixempra® Package Insert, Bristol-Meyers Squibb, *available at* http://packageinserts.bms.com/pi/pi_ixempra.pdf

[110] *See, e.g., Teva Pharms., USA, Inc. v. FDA*, 182 F.3d 1003, 1004 (D.C. Cir. 1999) ("Because we conclude that the FDA's refusal was arbitrary and capricious inasmuch as the FDA has taken an inconsistent position in another case and failed to explain adequately the inconsistency, we reverse and remand the case to the district court to determine anew whether injunctive relief is appropriate."); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 28 (D.D.C. 1997) ("If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the APA.").

B. FDA'S PRIOR RELIANCE ON DISEASE PROGRESSION ENDPOINTS IN FIRST-LINE MBC WAS APPROPRIATE.

PFS should be an accepted objective measure of treatment effect in first-line MBC reflecting a direct clinical benefit. PFS measures tumor control and facilitates clinical trials with reasonable sample sizes and follow-up times. PFS can be reliably measured using radiographs,[111] and potential investigator bias in assessing PFS can be minimized by implementing a placebo control and/or employing an independent review of tumor assessments (as was done in E2100).

FDA itself has recognized in guidance that PFS can be an endpoint for approval because PFS reflects tumor control, can be assessed before the determination of a survival benefit, is not confounded by subsequent therapy, and is generally based on objective and quantitative assessment.[112] The European Union's Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr.2) recognizes PFS as a primary endpoint for drug approval in oncology clinical studies.[113]

Most fundamentally, PFS is a valid measure of direct clinical benefit because prolonging the time to disease progression is clinically meaningful for patients. As noted by Dr. Marisa Weiss on behalf of Breastcancer.org, "[t]hrough ten years of dialogue with women diagnosed with metastatic breast cancer, Breastcancer.org has learned a great deal from these women about their feelings, perspectives, needs, and experiences with the disease and treatments … Longer progression-free survival is a meaningful benefit for many women."[114] Because MBC is an incurable

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[111] Therasse P, Arbuck SG, Eisenhauser EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.

[112] U.S. Food and Drug Administration, Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007) at 6, 8.

[113] European Medicines Agency, Guideline on the Evaluation of Anticancer Medicinal Products in Man at 16 (15 December 2005), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017748.pdf (last visited 14 January 2011) ("Acceptable primary endpoints include OS and PFS/DFS. …In situations where there is a large effect on PFS, a long expected survival after progression, or a clearly favourable safety profile, precise estimates of OS may not be needed for approval. … PFS is an acceptable endpoint in situations where it is expected that further lines of treatment with effect on OS may importantly hamper the detection of a relevant treatment effect on OS.").

[114] Letter from Dr. Marisa Weiss on Behalf of Breastcancer.org to ODAC Members (16 December 2010), *available at*

disease, the therapeutic goals for patients with MBC focus on maintaining tumor control, extending the time to subsequent progression, and delaying the introduction of subsequent lines of therapy.[115] PFS is inherently relevant to these goals.

Lengthening PFS delays the onset of disease-related symptoms and the side effects from new therapy. It also avoids the psychological consequences associated with disease progression and changing therapies, and eliminates uncertainty as to whether additional treatments will be effective.

Finally, the clinical significance of PFS effects can be supported by other related measures, such as 1-year survival. One-year survival reduces confounding of treatment effect by use of subsequent therapies, making it less subject to dilution of treatment effect than OS in an indication in which post-progression survival is long; and 1-year survival may result in faster access to Phase III results and approval of new therapies.[116] A 1-year survival result supporting a positive PFS effect also reflects safety and is clinically meaningful in the first-line setting.[117]

C. DEMONSTRATING A DIRECT EFFECT ON OVERALL SURVIVAL IS INCREASINGLY DIFFICULT IN FIRST-LINE MBC.

The requirement of an OS improvement as a measure of drug effect instead of PFS or other disease progression endpoints risks discarding a clinically meaningful treatment result in the first-line MBC setting. Additionally, although Genentech recognizes and agrees that the ultimate goal of treatment is to prolong survival, there are fundamental challenges with demonstrating that a first-line treatment for MBC improves OS.

The administration of second-line and beyond anti-cancer treatments, with their associated safety and efficacy effects, following a patient's initial disease

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http://www.breastcancer.org/about_us/press_room/press_releases/2010/fda_avastin.jsp (last visited 14 January 2011).

[115] Telli ML, Carlson RW. Clin Breast Cancer 2009; Beslija S, et al. Ann Oncol 2009; Cardoso F, et al. J Natl Cancer Inst 2009.

[116] Scientific discussion paper: Overall survival in clinical studies of first-line treatment for metastatic breast cancer at 14–15.

[117] Verma S, McLeod D, Batist G, et al. In the end what matters most? A review of clinical endpoints in advanced breast cancer. Oncologist. Epub 6 January 2011.

progression creates one challenge. Once a patient's cancer progresses while on treatment, it is generally necessary on ethical grounds to permit the patient to be treated with whatever therapy the treating physician considers best available care.[118] For purposes of the clinical trial, the administration of subsequent treatment lines outside the original, controlled study treatment arms may obscure the effect of the initial treatment on the patient's ultimate survival. This is particularly true where the duration of overall survival is long relative to the period of progression-free survival.

A systematic review of 76 randomized clinical trials for MBC, including 45 studies that enrolled only first-line patients, showed that approximately two-thirds of the overall survival time for MBC patients is accounted for by post-progression survival (i.e., survival after initial disease progression).[119] Stated differently, only about one-third of the duration of an MBC patient's overall survival occurs prior to progression on first-line treatment. Notably, the clinical trials that have shown an OS benefit in MBC were more likely to enroll patients who had progressed on prior therapy for metastatic disease. Of the 13 trials that had published improvements in both PFS and OS, 9 enrolled patients who had previously received treatment for metastatic disease, whereas only 4 of the trials included only first-line patients.[120]

Another challenge is provided by the fact that it is not typical to observe a larger *absolute* improvement in OS than in PFS with any new therapy, and this effectively translates into a smaller *percent* improvement in OS that is more difficult to detect. In other words, one would expect the magnitude of prolongation in OS in months to be similar to the magnitude of improvement of PFS in months. Actual clinical trials in first-line MBC confirm this to be a valid assumption, as the duration of post-progression survival (time from median PFS to median OS) has been similar or slightly longer in the control arm than in the corresponding experimental arm in 33 randomized studies in MBC.[121] Furthermore, median OS in recently conducted

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[118] American Cancer Society, Inc., Breast Cancer Facts & Figures 2009–2010, *available at* http://www.cancer.org/acs/groups/content/@nho/documents/document/f861009final90809pdf.pdf (last visited 14 January 2011).

[119] Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. J Clin Oncol 2010;28:1958–62.

[120] *Id*.

[121] Bowater RJ, Bridge LJ, Lilford RJ. The relationship between progression-free and post-progression survival in treating four types of metastatic cancer. Cancer Lett 2008;262:48–53. (III.C).

first-line studies of patients with HER2-negative MBC is 24 months or longer,[122] resulting in median post-progression survival of 18 months or more.

These challenges have made it increasingly difficult to conduct a controlled clinical study powered to show an effect on OS. Specifically, Broglio and Berry estimated the impact on sample size to detect an OS benefit assuming that a novel agent has a 3-month improvement in PFS (from 6 to 9 months), with no further incremental survival improvement beyond progression, under varying assumptions of the duration of survival after progression.[123] They found that longer duration of survival after progression led to greater dilution of the OS hazard ratio, and a study designed to detect this OS benefit with conventional statistical power would need to have 1050 to 2440 patients if the median survival after progression was between 12 and 24 months.

Assuming a typical patient accrual rate of 30 patients a month, this could result in a study that requires more than 6 years to accrue, 5 years longer than a typical 600-patient study designed to detect a PFS benefit. Similarly, simulations performed by Genentech, under the assumption of a larger 4-month treatment benefit in PFS and median duration of post-progression survival of 18 months (typical of studies of chemotherapy for first-line treatment of HER2-negative MBC), found that detection of an OS effect could require up to 2300 patients and take up to 7.5 years to deliver OS results.[124] These illustrative examples demonstrate the increasing difficulty of conducting a controlled clinical study in the first-line setting that is powered to show an effect on OS.[125]

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[122] Verma S, et al. Oncologist. Epub 6 January 2011.

[123] Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 2009;101:1642–9.

[124] Scientific discussion paper: Overall survival in clinical studies of first-line treatment for metastatic breast cancer at 10–14.

[125] Agents that have recently demonstrated an OS benefit in clinical trials in MBC are not to the contrary. Halaven™ (eribulin) was approved based on a Phase III trial in third-line MBC that showed a 2.5-month improvement in OS (HR=0.81, p=0.049) (2.7-month improvement at updated analysis, HR=0.81, p=0.014) and a non-statistically significant 45-day improvement in PFS (HR=0.87, p=0.14). Median OS in the control arm was 10.6 months, less than half of the 24.8 month median OS in the E2100 control arm. OS can be more easily demonstrated in the third-line and later settings because of the considerably shorter median OS observed in later treatment settings. Halaven™ Summary Basis of Approval, *available at*

The data and analyses presented above show that although OS remains the ultimate goal of MBC treatments, there are substantial scientific limitations on the ability to detect a significant OS benefit in studies of first-line treatments for MBC. In addition, strict adherence to an OS improvement standard risks discarding clinically meaningful treatments. For example, drugs that have been approved for MBC over the last 20 years have contributed to cumulative survival benefits, although the magnitude of improvements in disease progression endpoints for these drugs has been modest. Over the past decade, incremental improvements in survival have been achieved in the MBC setting, as shown in Figure 2.

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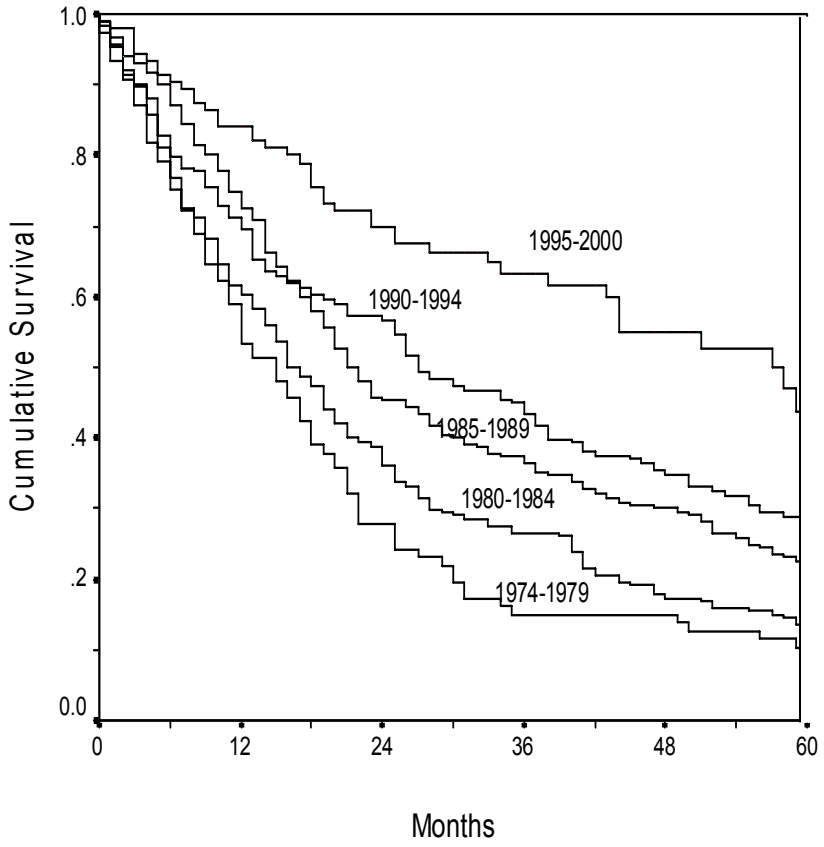
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201532s000_halaven_TOC.cfm (last visited 14 January 2011).

The investigational compound iniparib was studied in a Phase II trial in combination with Gemzar® and carboplatin in second- and first-line, triple-negative MBC with a 4.6-month improvement in OS (HR = 0.57, p = 0.01) and a 2.3-month improvement in PFS (HR = 0.59, p = 0.01). Median OS was 7.7 months in the control arm (compared with 22.8 to 31.9 months in the control arms of RIBBON1, AVADO, and E2100). Median PFS was brief also, 3.6 months in the control arm (compared with 5.7 to 8.0 months in the control arms of RIBBON1, AVADO, and E2100). Iniparib is currently being studied in a phase III trial adequately powered to evaluate OS and PFS. J. O'Shaughnessy, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. New Engl J Med. Epub 5 January 2011; Carey LA, Sharpless NE. PARP and cancer—if it's broke, don't fix it. New Engl J Med. Epub 5 January 2011.

Figure 2
Survival of Patients with MBC: 1974–2000[126]



This improvement in survival has occurred despite the fact that few randomized trials have demonstrated more than a modest effect on disease progression or an effect on OS. That is, few individual therapies have been shown in clinical trials to confer a disease progression benefit with a magnitude comparable to that observed in E2100, or a clear OS benefit, but median survival of MBC patients has nonetheless improved.

This analysis indicates that it may not be necessary to require a direct showing of increased OS for individual agents in order to extend survival ultimately for MBC

[126] Giordano SH, Buzdar AU, Smith TL, et al. Is breast cancer survival improving? Trends in survival for patients with recurrent breast cancer diagnosed from 1974 through 2000. Cancer 2004;100:44–52. *See also* 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.

patients. In addition, to the extent that FDA's new proposed efficacy standard would prevent the future approval of drugs based on comparable showings to those made in past years, FDA might jeopardize the extension of the survival gains that have been observed going forward. Whereas therapeutic agents came to market previously with more modest showings of clinical benefit but nonetheless contributed to the overall improvement in outcomes for MBC patients, new agents may never make it to the market or be allowed to stay on the market under FDA's new standard.

D. FDA IS NOT APPLYING A CLEAR AND CONSISTENT STANDARD.

FDA has effectively declared that an effect on PFS demonstrates meaningful clinical benefit only when it is of sufficiently large magnitude, but has not made clear how much improvement of median PFS is required in the first-line MBC setting. FDA's actions on Avastin suggest that an improvement of 5.5 months (HR=0.48) (as in E2100) is adequate, but an improvement of 2.9 months (HR=0.69) (as in the independently powered capecitabine comparison of RIBBON1) is not adequate. But FDA has not indicated where in the range between 2.9 months and 5.5 months the magnitude of PFS improvement would transition from inadequate to adequate, and more importantly, FDA has not articulated its rationale for this judgment. FDA therefore has failed to set forth a clear and coherent framework for sponsors to follow.

Moreover, FDA has created this new standard by way of action on an individual application, with no effort to provide broader transparency beyond direct application of the new standard to Avastin. Even with respect to Avastin, FDA was not clear about its expectations. FDA accepted AVADO and RIBBON1 as confirmatory studies, with PFS as the primary endpoint and OS as a secondary endpoint, without establishing a particular magnitude of change in PFS that would need to be demonstrated.

In a 26 February 2009 Type B meeting, FDA acknowledged that AVADO and RIBBON1 were not designed with OS as a primary endpoint and thus the sponsor would not expect to observe a significant effect on OS.[127] In a 6 March 2009 follow-up call to the 26 February 2009 Type B meeting, FDA then clarified that "the

[127] Minutes, 26 February 2009 Type B Meeting at 3.

basis for conversion to full approval will be demonstrated improvement in progression-free survival and evidence that survival will not be impaired."[128] FDA *did not establish a required magnitude of median PFS improvement* for AVADO or RIBBON1, or reference a range for the magnitude of improvement in median PFS that would be acceptable depending on the presence of an OS trend or benefit.[129]

Since the 20 July 2010 ODAC meeting, FDA has stated the standard differently. At the ODAC meeting, Dr. Pazdur asserted that "as a condition of accelerated approval, Genentech was required to submit data from two on-going placebo-controlled trials, AVADO and RIBBON1, to confirm the *magnitude* of the treatment effect on PFS and to provide additional information on the effects on overall survival."[130] Similarly, in its Decision Memorandum, FDA indicated that "the continued marketing of Avastin for the metastatic breast cancer indication was contingent upon either an improvement in PFS of *a similar magnitude as noted in E2100* or an improvement in OS in the AVADO and RIBBON1 trials."[131]

FDA's recent change in approach is also evident in its general characterization of PFS as an endpoint. At the time of Avastin's accelerated approval for MBC, Dr. Pazdur explained:

> [Avastin's] accelerated approval should not be interpreted as a change in regulatory policy regarding cancer drug approvals. Three other breast cancer drugs—Taxol, lapatinib and ixabepilone—were approved because of their ability to stop the progression of tumors. We still believe that overall survival remains the gold standard for cancer drug approval, but delaying the progression of a tumor may in itself be a clinical benefit.[132]

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[128] Minutes, 26 February 2009 Type B Meeting at 7.

[129] In its Decision Memorandum, FDA notes that AVADO and RIBBON1 were not reviewed under a Special Protocol Assessment ("SPA") and that the agency did not agree on the primary endpoints prior to trial initiation. FDA nonetheless had an opportunity to review the trial designs prior to accepting AVADO and RIBBON1 as the confirmatory studies. If FDA deemed the trial designs inappropriate, the agency had the opportunity to require different studies. It did not do so.

[130] Transcript, 20 July 2010 ODAC at 14 (emphasis added); *see also id.* at 12 ("[T]he magnitude of PFS improvement, especially if not supported by an improvement in overall survival, should be substantial, clinically meaningful and be able to be replicated in additional trials.").

[131] Decision Memorandum at 4 (emphasis added).

[132] With Avastin Approval For Breast Cancer, Will More Patients Hit Price Cap?, The Pink Sheet, 3 March 2008. In an interview discussing the accelerated approval of Avastin's MBC indication,

As recently as the July 2010 ODAC meeting, FDA commented that "progression-free survival may be considered … a direct clinical benefit."[133] Now, in its Decision Memorandum, FDA states that it considers "PFS as a surrogate endpoint of clinical benefit rather than a direct measure of clinical benefit" and that there is an "indirect relationship of an improvement in PFS to clinical benefit."[134]

Prior to this NOOH, the standards for withdrawal of products marketed under accelerated approval were already unclear. A recent GAO report recommended that FDA "[c]larify the conditions under which the Agency would utilize its authority to expedite the withdrawal of drugs approved based on surrogate endpoints under the accelerated approval process if sponsors either fail to complete required confirmatory studies with due diligence, or if studies are completed, but fail to demonstrate the clinical effectiveness of the drugs."[135] FDA's proposal to withdraw Avastin's indication for MBC—on the basis of a standard that FDA never previously communicated to Genentech or the broader public, and which stems from a conclusion that cuts against the determinations made by clinical experts and other regulatory bodies based on the same data—may further muddle sponsors' understanding of what is required to utilize the accelerated approval pathway successfully and thereby deter the development of novel therapies.

Patient advocates recognize the potential impact of FDA's decision on Avastin for drug development in MBC. On 17 August 2010, Susan G. Komen for the Cure and

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Dr. Pazdur stated: "PFS is a clinical benefit in the right context. In this case, a robust delay in progression accompanied by a doubling of response rate was considered a benefit to patients facing a progressive, incurable disease. … Skeptics cite that PFS has not been linked to symptom benefits or quality of life. These relationships are difficult to prove. Most oncology trials are unblinded; hence, the evaluation of symptoms and health-related quality of life may be unreliable." Dr. Pazdur went on to state: "Since survival is both a safety and efficacy endpoint, we must have assurance that there is no detrimental survival effect. … To state that we would never approve a drug unless it demonstrated a statistically significant effect on overall survival is overly rigid. Although all agree that an improvement in overall survival is the 'gold standard,' many—including patients, oncologists, and drug regulators—have voiced that a delay in progression … may be of clinical benefit." PFS Is a Benefit 'in the Right Context,' Pazdur Says in Q&A on Avastin Approval, The Cancer Letter, 29 February 2008 at 3.

[133] FDA, Briefing Book, 20 July 2010 ODAC at 5; *see also id.* at 9 (noting that at the 5 December 2007 ODAC "[m]any committee members agreed that PFS is a clinically meaningful endpoint").

[134] Decision Memorandum at 4, 5.

[135] GAO Report at 36.

the Ovarian Cancer National Alliance issued a joint statement urging that Avastin be kept on the market for current patients and expressed concern for "the message that this decision sends about drug development in women with advanced breast cancer … We hope that drug manufacturers will continue to develop medications for the treatment of metastatic breast cancer, and would not want this decision to mean that drug development for breast cancer comes to a crashing halt."[136]

Leading clinicians express similar concerns, not only for drug development in MBC, but also for oncology drugs more generally. According to Dr. Adam Brufsky at the University of Pittsburgh:

> The issue I have is how the FDA might disapprove a drug without any new safety signal that anyone knows of, and that has met its primary efficacy end point … I'm a little concerned about the development of future oncology products if the FDA decides midstream to change the end point for approval, which may or may not be done in this case. But it is cause for concern … PFS was the primary end point in the studies; OS was a secondary end point.[137]

The potential perils of FDA's current actions for drug development are thus threefold. First, FDA is applying a standard that prior drugs generally would not have met and that future drugs may have difficulty meeting. Second, FDA has not clearly specified what magnitude of PFS benefit it would find clinically meaningful, nor has it explained its rationale for that magnitude. Third, FDA has not acted consistently, because FDA is recommending termination of accelerated approval for the study (E2100) which has in fact demonstrated the largest magnitude of PFS improvement that FDA has ever reviewed in MBC to date and is doing so without setting clear expectations for the sponsor *ex ante*.

[136] Avastin May Trigger Two FDA Decisions: One on Approval, Another on Withdrawal, The Cancer Letter, 3 September 2010 at 5.

[137] Avastin Controversy Shakes up Oncology Community, Clinical Oncology News, October 2010.

IV. THE APPROPRIATE OUTCOME IS TO MAINTAIN ACCELERATED APPROVAL FOR AVASTIN WITH PACLITAXEL TO PRESERVE PATIENT CHOICE.

A. CONFLICTING INTERPRETATIONS OF DATA SHOULD BE RESOLVED IN FAVOR OF RETAINING ACCESS AND CHOICE.

In adopting the accelerated approval regulations for biological products, FDA anticipated that studies in which the effectiveness data are disputed would be among the more difficult situations that the Agency would face in implementing the accelerated approval withdrawal provisions:

> The [ ] regulations provide for an expedited procedure to withdraw approval; they do not guarantee that results of studies will be wholly unambiguous or that FDA will always be able to prevail in its view as to the need for withdrawal … data that are ambiguous will inevitably lead to difficult judgments.[138]

The challenge presented here is heightened because there is scientific debate about what measure of benefit is clinically meaningful for the incurable disease of MBC and what degree of PFS benefit supports the use of a therapy in the first-line setting. The regulatory history of Avastin in MBC reflects FDA's struggle to identify appropriate endpoints for clinical studies from which the Agency is called on to make complex benefit–risk determinations.

The very fact that FDA's determination has been so difficult supports continued accelerated approval. That is, given the differences of opinion surrounding the appropriateness of PFS as a clinical endpoint in first-line MBC and the conclusions to be drawn from the PFS data for Avastin, FDA's presumption should be to maintain accelerated approval, while Genentech performs a confirmatory trial in combination with paclitaxel. This approach recognizes the intent of the accelerated approval scheme, which is to encourage the development and availability of drugs that treat serious diseases and address unmet needs, and to expand treatment options for clinicians and patients. Indeed, some commentators have expressed concern that the Agency is not sufficiently fulfilling the purpose of the accelerated approval pathway.[139]

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[138] 57 Fed. Reg. at 58956.

[139] *See, e.g.,* Richey EA, Lyons EA, Nebeker JR, et al. Accelerated approval of cancer drugs: improved access to therapeutic breakthroughs or early release of unsafe and ineffective drugs? J Clin

B. WITHDRAWAL IS NOT LEGALLY JUSTIFIED AND WOULD BE INCONSISTENT WITH FDA PRECEDENT.

1. The Legal Standard for Withdrawal Has Not Been Met.

Withdrawal of accelerated approval is appropriate when "a post-approval study … fails to verify clinical benefit" or "other evidence demonstrates that the fast-track product is not safe or effective under the conditions of use."[140] The data supporting the use of Avastin in first-line MBC do not fulfill this standard for withdrawal.

FDA accepted the designs of AVADO and RIBBON1 with PFS as the primary endpoint (and in the case of AVADO knowing the PFS results), when it designated the studies as the postmarketing commitments at the time of accelerated approval. These post-approval studies verified and further defined the clinical benefit observed in E2100 by delivering consistent, reliable, and statistically significant demonstrations of improvements in PFS. These data also demonstrated that the safety profile of Avastin in MBC is consistent with that observed in other indications and described in the Avastin® U.S. Package Insert. For purposes of withdrawal under FDCA Section 506 and 21 C.F.R. § 601.43, it is not reasonable or appropriate to conclude that these studies failed to verify clinical benefit, or that these studies constitute "other evidence" demonstrating that the product is not safe or effective under the conditions of use, when the studies met their pre-defined and agreed-upon endpoints.

Oncol 2009;27:4398–405 (noting that "[a]nother concern is that obtaining [accelerated approval] has become more difficult recently," and finding that accelerated approvals accounted for 78% of oncology new molecular entities (NMEs) approved for marketing between 2001–03, but only 32% of oncology NMEs from 2004–08).

[140] FDCA § 506(b)(3)(B)-(C); 21 C.F.R. § 601.43(a)(1) and (a)(6).

Even if AVADO and RIBBON1 do not verify the clinical benefit of Avastin with a broader range of chemotherapy agents (determined by a substantial magnitude of effect on PFS), there is no basis for FDA to conclude that these studies fail to verify the clinical benefit of Avastin with paclitaxel. FDA itself has acknowledged that even if a postmarketing study fails to verify clinical benefit broadly, there are various grounds for maintaining approval, including where there are "unforeseen limitations in trial design" and where "there may be a subset of patients for whom the drug may nevertheless be effective."[141]

E2100 showed that there is a substantial PFS benefit for those patients for whom paclitaxel is an appropriate chemotherapy backbone for first-line therapy. AVADO and RIBBON1 enrolled patients for whom other chemotherapy backbones were suitable, and the smaller magnitudes of the PFS benefit observed in those studies do not impeach the effectiveness of Avastin for patients for whom paclitaxel is indicated. As outlined earlier, the available evidence suggests that the choice of chemotherapy may matter with respect to the magnitude of effect to expect from Avastin.

FDA's acknowledgment of future off-label use of Avastin in MBC further indicates that withdrawal is inappropriate. Recent statements by FDA leaders suggest that the Agency is relying on Avastin's other approved indications to reassure patients that Avastin will not be completely unavailable in MBC. For example, in a letter to the breast cancer community, FDA stated, "This recommendation does not affect Avastin's other approved indications to treat advanced colon, lung, kidney, and brain cancers. As long as Avastin is on the market, the law allows doctors to prescribe it for any use—even if the use is not formally FDA-approved."[142] This tacit support for the off-label use of Avastin is inconsistent with FDA's proposal to withdraw the MBC

[141] GAO Report at 61 (noting that "FDA must also consider the possibility that, despite results form confirmatory studies that may appear to indicate that a drug does not provide clinical benefit, there may be a subset of patients for whom the drug may nevertheless be effective").

[142] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Breast Cancer Community (16 December 2010), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237286.pdf (last visited 14 January 2011); Alicia Mundy, Regulator Defends Avastin Decision, FDA says Genentech Was Warned of Inadequate Trial Data before Agency Revoked Its Approval for Use in Breast Cancer, The Wall Street Journal, Epub 6 January 2011 ("Doctors can still prescribe Avastin, since it retains its approval for four other cancers including colon and lung cancer, said Dr. Pazdur.").

indication. Withdrawal constitutes a determination that Avastin should not be available for MBC because the benefit–risk profile is unfavorable; yet FDA's statements acknowledging the likelihood of off-label use recognize that Avastin may be beneficial for some patients and that patients and physicians regard Avastin as an important choice for women with MBC.

Moreover, this approach of relegating Avastin's use in MBC to off-label use does not further the public health. In fact, when FDA granted Avastin accelerated approval in 2008, the Agency recognized the importance of providing patients and clinicians with prescribing information to help them make treatment decisions grounded in data. Dr. Pazdur stated at that time:

> Since Avastin was an approved drug, many patients with breast cancer were being treated with the drug 'off label.' FDA has long held that a reason to encourage sponsors to submit supplemental BLAs/NDAs is [to] provide both the patient and physician with prescribing information that the agency has reviewed. The Avastin prescribing information now includes FDA-reviewed safety and efficacy data for breast cancer.[143]

FDA should not change its view on this issue.

Finally, this means of reassuring patients about the potential for continued access to Avastin is misleading, as payors may opt to terminate or limit reimbursement for Avastin in MBC as a consequence of FDA's withdrawal. One Medicare contractor has in fact considered such a step.[144]

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[143] PFS Is a Benefit 'in the Right Context,' Pazdur Says in Q&A on Avastin Approval, The Cancer Letter, 29 February 2008.

[144] Palmetto GBA, a regional Medicare contractor, initially announced that it would no longer pay for the use of Avastin to treat breast cancer starting on 29 January 2011, which "appear[ed] to go against assurances given by F.D.A. officials last month that the Centers for Medicare and Medicaid Services would not consider changing reimbursement for Avastin until Genentech had exhausted its appeals." Andrew Pollack, Medicare Coverage for Breast Cancer Drug Ends in Some States, New York Times Prescriptions Blog (6 January 2001), *available at* http://prescriptions.blogs.nytimes.com/2011/01/06/medicare-coverage-for-breast-cancer-drug-ends-in-some-states/ (last visited 14 January 2011). The next day, Palmetto GBA reversed its position and indicated that it would continue to pay for Avastin for the time being while Genentech appealed FDA's decision to withdraw approval of Avastin. Andrew Pollack, Medicare Contractor Will Pay for Avastin during Appeal, New York Times Prescriptions Blog (7 January 2001), *available at* http://prescriptions.blogs.nytimes.com/2011/01/07/medicare-contractor-will-pay-for-avastin-during-appeal/ (last visited 14 January 2011).

2. Withdrawal of Avastin's MBC Indication Would Depart Significantly from Other Withdrawals of Accelerated Approval.

It would be unprecedented for FDA to withdraw accelerated approval where the sponsor duly conducted the required post-approval studies and where those studies met their agreed-upon endpoints with no new safety signals arising. For the three products where FDA previously has sought withdrawal of accelerated approval—Mylotarg® (gemtuzumab ozogamicin), Ethyol® (amifostine), and Iressa® (gefitinib)—the postmarketing studies clearly failed to meet their endpoints, and in one instance, a study identified new fatal risks. Mylotarg® was voluntarily withdrawn from the market after the confirmatory study showed a significant increase in treatment-related deaths and no improvement in disease-free survival with the addition of Mylotarg® to chemotherapy.[145] Ethyol® was voluntarily withdrawn after a confirmatory study failed to demonstrate that the drug did not affect the efficacy of the paired chemotherapy drug.[146] Although the sponsor of Ethyol® was given the opportunity to do a second confirmatory trial, the trial was deemed infeasible and was never conducted.[147] The label of Iressa® was limited severely to patients already on and benefiting from the drug—a *de facto* withdrawal—after the confirmatory study failed to meet its primary endpoint.[148]

The data for Avastin in first-line MBC stand in marked contrast to the data generated for Mylotarg®, Ethyol®, and Iressa®. Avastin's confirmatory studies, AVADO and RIBBON1, met their primary endpoints with statistically robust improvements in PFS,

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[145] Press Release, FDA, Pfizer Voluntarily Withdraws Cancer Treatment Mylotarg from U.S. Market (21 June 2010), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm216448.htm (last visited 14 January 2011); FDA, Gemtazumab Ozogamicin, www.fda.gov/AboutFDA/CentersOffices/CDER/ucm216790.htm (last visited 14 January 2011).

[146] MedImmune Oncology, Inc., Briefing Book, 12 March 2003 ODAC at 4–5, *available at* http://www.fda.gov/ohrms/dockets/ac/03/briefing/3936B1_05_MedImmune-Eythol.pdf (last visited 14 January 2011).

[147] *Id.* at 15; Transcript, 8 November 2005 ODAC, at 28, *available at* http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4191T1.pdf (last visited 14 January 2011).

[148] FDA, New Labeling and Distribution Program for Gefitinib (Iressa) (17 June 2005), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm163112.htm (last visited 14 January 2011). *See also* FDA, Questions and Answers on Iressa (Gefitinib) (17 June 2005), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110476.htm (last visited 14 January 2011).

without detriment to OS, and no new safety signals; and an additional confirmatory study is feasible. Withdrawal under these circumstances is unjustified and would be inconsistent with FDA precedent. The absence of a single instance in which FDA has withdrawn approval of a drug where the required postmarketing studies reached their primary endpoints and no new safety signals were identified underscores that the legal standard for withdrawal has not been met.

C. FURTHER STUDY CAN CLARIFY THE CLINICAL BENEFIT OF AVASTIN IN MBC.

1. Genentech Is Prepared to Conduct a Confirmatory Study of Avastin with Paclitaxel Incorporating a Pre-Specified Biomarker Component.

Following the 20 July 2010 ODAC meeting, Genentech submitted a proposal to FDA for a confirmatory study of Avastin: a double-blind, randomized, multicenter, Phase III study designed to characterize further and confirm the efficacy and safety of Avastin in combination with paclitaxel, as shown by E2100. PFS would be the primary efficacy endpoint, and OS, 1-year survival, and response rate would be secondary efficacy endpoints.

This study would include a biomarker component to identify patients who may be more likely to derive a more substantial benefit from Avastin. As presented by the investigators at the December 2010 San Antonio Breast Cancer Symposium, recent data analyses from AVADO suggest that plasma VEGF-A may be a potential predictive marker for Avastin activity.[149] Patients with high levels of VEGF-A had a PFS hazard ratio of 0.49 (standard dose), whereas patients with low levels of VEGF-A had PFS hazard ratio of 0.86. This finding suggests that patients with high levels of VEGF-A may be more likely to derive a more substantial benefit from Avastin. The relevance of VEGF-A is scientifically plausible given Avastin's inhibitory activity on the biologic actions of VEGF.

A biomarker program has been an integral part of Genentech's research on Avastin. A large number of markers (over 10,000 in preclinical and over 100 in clinical

[149] Miles DW, de Haas SL, Dirix L, et al. Plasma biomarker analyses in the AVADO Phase III randomized study of first-line bevacizumab + docetaxel in patients with human epidermal growth factor receptor (HER) 2-negative metastatic breast cancer [abstract]. SABCS, *available at* http://www.abstracts2view.com/sabcs10/view.php?nu=SABCS10L_939&terms (last visited 14 January 2011).

studies) have been studied in a variety of tumor types (including MBC, pancreatic cancer, gastric cancer, colorectal cancer, lung cancer, and brain cancer) for prognostic and predictive biomarkers. These biomarkers include plasma and tumor markers, circulating endothelial and progenitor cells, imaging, and genetic polymorphisms. In Phase III trials of Avastin, using a first-generation VEGF assay, VEGF was a strong prognostic—but not predictive—marker for Avastin's efficacy. However, using a second-generation VEGF test, VEGF at baseline demonstrated a potential predictive effect in MBC and pancreatic cancer for patients with samples available.

Many stakeholders have recognized the utility of identifying those patients who are likely to derive a benefit from Avastin, including members of the 20 July 2010 ODAC. For example, Dr. Patrick Loehrer noted

> I do think there is activity for Avastin in breast cancer. I think it is yet to be clarified. … I also would welcome them to identify that patient population that may benefit. I think, again, there are some likely markers out there. … I think to make this a great drug … I think we need to decide who we shouldn't treat and treat those who are going to benefit.[150]

Similarly, Dr. Gregory Curt commented that

> [W]hat we don't have is the ability to predict who is going to benefit from this drug and who's going to have the toxicities. That would probably be the next phase of the research with this agent … I think if we had ways to predict who would benefit and who would have toxicities, this wouldn't be such a difficult discussion.[151]

Finally, Dr. Gary Lyman stated

> I would hope there would be opportunities for the company to come back with some robust quality of life data and some further exploratory data in identifying patients most likely to benefit from the Avastin therapy. Or, on the other hand, more likely to have toxicity and should not be treated.[152]

[150] Transcript, 20 July 2010 ODAC at 227–28.

[151] Transcript, 20 July 2010 ODAC at 179.

[152] Transcript, 20 July 2010 ODAC at 209.

Patient advocates have also expressed support for further research to identify patients who are more likely to derive benefit from Avastin. For example, Elizabeth Thompson, President, Susan G. Komen for the Cure, has stated

> We are also urging Genentech/Roche to continue research on a biomarker for Avastin to determine which women will benefit from the drug. … As a patient advocate organization, we call on all stakeholders—government, private industry, academia and the nonprofit community—to invest in the development of biomarkers and new drugs and to get the new technology and treatments to patients' bedsides as safely and as quickly as possible.[153]

Leading oncologists confirm that, in their experience, there are breast cancer patients who derive genuine benefit from treatment with Avastin.[154] For example, Dr. Eric P. Winer at Harvard Medical School has stated, "This is not a worthless drug by any means. There is almost certainly a group of women who get a big benefit."[155] Likewise, Dr. Julie Gralow, of the Fred Hutchinson Cancer Research Center, attests, "I am certain that there is a population of breast cancer patients who are getting real benefit … I don't think PFS of 12 months is a fluke in E2100." [156] Dr. Gralow also expresses the view that "[t]o withhold this drug from all patients because some don't benefit is incorrect."[157] The goal of the biomarker component of the proposed

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[153] Press Release, Susan G. Komen for the Cure, Susan G. Komen for the Cure Encourages Continued Coverage for Avastin For Breast Cancer Patients Who Are Benefiting From the Drug (16 December 2010), *available at* http://ww5.komen.org/KomenNewsArticle.aspx?id=6442452909 (last visited 14 January 2011).

[154] *See, e.g.*, Amanda Gardner, FDA Advises against Avastin as Treatment for Breast Cancer; but Patients Won't Be Affected for Now, FDA Says, Healthday News, 16 December 2010, *available at* http://consumer.healthday.com/Article.asp?AID=647609 (last visited 14 January 2011) (quoting Dr. Neil Spector, professor of medicine at Duke Cancer Institute as stating: "There are women who have clearly responded to the treatment"); Press Release, American Cancer Society, FDA Begins Process to Remove Indication for Avastin For Metastatic Breast Cancer: Response from Dr. Len Lichtenfeld (16 December 2010), *available at* http://pressroom.cancer.org/index.php?s=43&item=284 (last visited 14 January 2011) ("What we clearly need is a way for doctors to more accurately predict which women will have a better chance of benefiting from this important targeted therapy.")

[155] Rob Stein, FDA Considers Revoking Approval of Avastin for Advanced Breast Cancer, The Washington Post, 16 August 2010; A01.

[156] Avastin May Trigger Two FDA Decisions: One on Approval, Another on Withdrawal, The Cancer Letter, 3 September 20 at 3–4.

[157] Amanda Gardner, FDA Advises against Avastin as Treatment for Breast Cancer; but Patients Won't Be Affected for Now, FDA Says, HealthDay News, 16 December 2010, *available at* http://consumer.healthday.com/Article.asp?AID=647609 (last visited 14 January 2011).

confirmatory study would be to identify those patients who are more likely to benefit from Avastin.

Moreover, the biomarker component advances FDA's efforts to encourage personalized medicine. FDA Commissioner Dr. Margaret Hamburg noted in remarks at the Personalized Medicine Coalition's Sixth Annual Keynote Luncheon on 25 February 2010 that "Clearly, we can have much better outcomes for patients if we can discern what distinguishes one [patient] group from another, in terms of positive response, and design a clinical trial based on that knowledge."[158]

As noted above, Genentech has extensive experience with and a strong commitment to biomarker research. And more generally, Genentech has a record of conducting robust and meaningful clinical studies. Commenting on AVADO and RIBBON1, members of the 20 July 2010 ODAC remarked

> "[W]e got two excellent, or should I say, outstanding clinical trials done in a reasonable period of time."[159]
>
> "The sponsor did perform excellent studies."[160]
>
> "I think the sponsor is to be commended for supporting the confirmatory studies."[161]

Genentech would apply its expertise and resources to conduct a confirmatory study with due diligence to determine the magnitude of benefit that patients can derive from Avastin in combination with paclitaxel and to evaluate further whether there is a valid predictive biomarker for patient benefit.

2. <u>Genentech Would Complement This Study with Steps to Convey Currently Available Data Regarding Avastin.</u>

Recognizing the concerns that FDA has raised about the benefit–risk profile for Avastin in MBC, Genentech would take several steps during the pendency of this

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[158] Bringing Home the Genome: the FDA's Role in Realizing Personalized Medicine, transcript of remarks, *available at* http://www.personalizedmedicinecoalition.org/sites/default/files/files/Hamburg%20Transcript.pdf (last visited 14 January 2011).

[159] Transcript, 20 July 2010 ODAC at 228 (statement of Dr. Wilson).

[160] Transcript, 20 July 2010 ODAC at 230 (statement of Dr. D'Agostino).

[161] Transcript, 20 July 2010 ODAC at 231 (statement of Dr. Richardson).

confirmatory study to ensure that patients and clinicians can make well-informed, data-driven decisions about whether to use Avastin. First, Genentech would clarify that the indication for use is only in combination with paclitaxel (not other chemotherapies) and Genentech would modify the Avastin labeling to reflect the current Avastin data in MBC. Genentech already has proposed certain modifications to FDA in this regard. Second, Genentech would continue the cessation of affirmative marketing of Avastin for MBC that the company voluntarily undertook as of 27 August 2010. Finally, Genentech would adopt a Risk Evaluation and Mitigation Strategy ("REMS") with a MedGuide and a special communication plan to support physicians and patients in making informed treatment decisions.

V. GENENTECH IS ENTITLED TO A HEARING.

Genentech seeks a hearing on the questions presented above. At this hearing, Genentech will produce evidence through witnesses of the efficacy data on Avastin, its safety data, its regulatory history, the relevant disease and treatment options, and the policy implications of the FDA's decision to withdraw accelerated approval for Avastin plus paclitaxel in MBC.

The regulations mandate such a hearing, without allowing for summary adjudication. But even if the summary adjudication standard from other portions of the Code of Federal Regulations ("C.F.R.") were applied, denial of a hearing would be improper here. The applicable regulatory standards are not precise, and there are demonstrated factual questions, including on issues FDA has not previously considered, regarding whether these standards are met. The significant public interest in the policy questions presented by this matter further highlights the necessity for a hearing.

A. THE GOVERNING REGULATIONS REQUIRE A HEARING.

FDA's proposal to withdraw the approval of Avastin for MBC is governed by 21 C.F.R. § 601.43 and 21 C.F.R. Part 15. These regulations do not permit FDA to deny a sponsor a hearing by finding a lack of a material factual dispute.

Instead, the regulations provide that, upon an applicant's timely request for a hearing on FDA's proposed withdrawal of accelerated approval, "the agency *will* publish a

notice of hearing in the Federal Register."[162] Contrary to FDA's assertions in the NOOH,[163] neither 21 C.F.R. § 601.43 nor Part 15 permits FDA to invoke summary judgment and deny a hearing on the ground that there are no "genuine and substantial issues of material fact." That summary judgment standard is provided in distinct and inapplicable portions of the regulations.[164]

A sponsor's unqualified right to a hearing on FDA's proposal to withdraw accelerated approval exists because the applicable withdrawal procedures are expedited and the hearing is significantly streamlined compared with the type that applies for the proposed withdrawal of a product with an ordinary approval.[165] FDA addressed these points when promulgating the withdrawal procedures provided under 21 C.F.R. § 601.43. Comments submitted to FDA on its proposed rule expressed concern that there would not be adequate due process to the sponsors prior to withdrawal. The Agency explained that "[t]hrough the hearing process in this final rule . . . applicants will be afforded the opportunity to present any data and information they believe to be relevant to the continued marketing of their product."[166] FDA offered similar assurances in response to questions about the potential "appearance of bias or preconceived notions" that might affect the withdrawal process, affirming that the:

> Commissioner's decision regarding withdrawal would not occur until after the applicant had an opportunity for hearing as described in those sections. The Commissioner would then expect to review the issues with objectivity and fairness *having had the benefit of the presentations and discussions at the hearing* and of the advisory committee's recommendations.[167]

The Agency's commentary confirms what is explicitly laid out in the regulations: FDA may not make the significant decision to withdraw approval for Avastin's indication for the treatment of an incurable disease without first providing Genentech a hearing.

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[162] 21 C.F.R. § 601.43(c) (emphasis added).

[163] NOOH at 4.

[164] *See, e.g.*, 21 C.F.R. §§ 314.200(g), 514.200(c), 601.7(a).

[165] *Compare* 21 C.F.R. part 15 *with* 21 C.F.R. parts 12, 16.

[166] 57 Fed. Reg. at 58955.

[167] *Id.* at 58957 (emphasis added).

B. GENENTECH MEETS EVEN DISCRETIONARY STANDARDS FOR A HEARING.

Assuming that FDA had the power to deny a hearing, it would be inappropriate to exercise that power on these facts: denial of a hearing is particularly inappropriate where the governing regulations are imprecise, Genentech has demonstrated ample factual questions suitable for a hearing, and policy concerns militate against denying a hearing.

1. A Hearing Is Required because the Regulatory Standards at Issue Here Are Imprecise.

Given the regulatory standards at issue here, the law and basic fairness require that Genentech have the benefit of a hearing before FDA takes the action proposed in the NOOH. In the landmark case of *Weinberger v. Hynson, Westcott & Dunning, Inc.*,[168] the Supreme Court explained that FDA may invoke its summary disposition authority only when the regulations on which it intends to rely are "precise."[169] Particularized regulations "provide the drug manufacturer with notice as to just what its submission must contain to warrant initial or continued authorization to market a drug."[170] Regulations fail the precision standard articulated in *Hynson* where they call for "the exercise of discretion or subjective judgment in determining whether," for example, a sponsor's study submitted in support of its application was "adequate and well controlled" or the method of selecting participants for a study provided "adequate" assurances that the participants were "suitable."[171] These "qualitative standards do not lend themselves to clear-cut definition" and may not be an appropriate basis for denying a hearing to an applicant.[172]

The principle expressed in *Hynson* is grounded in core fairness concerns: absent "detailed regulations dealing with the sort of data and methodological rigor that it will insist upon[,] . . . fairness to the regulated party set[s] . . . severe constraints on

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[168] 412 U.S. 609 (1973).

[169] *Id.* at 621 n.17.

[170] *American Cyanamid Co. v. FDA*, 606 F.2d 1307, 1313 (D.C. Cir. 1979).

[171] *Hynson*, 412 U.S. at 621 n. 17.

[172] *Id*.

FDA's authority to dispense with the statutorily-required hearings" on drug applications.[173]

Sections 601.43(a)(1) and 601.43(a)(6), the bases for FDA's proposed action here, reflect the type of "broad judgmental concepts"[174]—"clinical benefit" and "safe or effective under its conditions of use"—upon which summary disposition may not proceed. Neither of the provisions is sufficiently detailed to alert Genentech "to just what its submission must contain to warrant initial or continued authorization to market [its] drug."[175]

Genentech conducted "adequate and well-controlled" confirmatory studies pursuant to 21 C.F.R. § 601.41 to demonstrate Avastin's impact on PFS, the agreed-upon primary endpoint. The relevant regulations failed, however, to provide Genentech with notice that its confirmatory studies, all of which also demonstrated statistically significant improvement in PFS, would be deemed inadequate to "verify" Avastin's "clinical benefit" under 21 C.F.R. § 601.43(a)(1). Notably, 21 C.F.R. § 601.43(a)(1) does not specify the type, magnitude, or duration of clinical benefit Genentech would be required to demonstrate to avoid withdrawal.

Similarly, the mandate in 21 C.F.R. § 601.43(a)(6) that a drug must be "safe or effective under its conditions of use" to maintain approval is also insufficiently precise to justify summary adjudication. Section 601.43(a)(6) does not specify the nature, severity, likelihood, or frequency of adverse events that would form the basis for an Agency finding that Avastin is not "safe or effective under its conditions of use." It thus is insufficient to advise Genentech that Avastin's well-characterized (and unchanged) safety profile would be treated as presenting an intolerable risk of serious adverse events in light of the available efficacy data.

FDA itself has acknowledged the imprecise nature of its accelerated approval regulations. In response to the GAO's September 2009 report, FDA declined to

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[173] *American Cyanamid*, 606 F.2d at 1323; *see also Hess & Clark Div. of Rhodia, Inc. v. FDA*, 495 F.2d 975, 983 (D.C. Cir. 1974) ("[T]he [FDA's] 'summary judgment' regulations and procedures must be applied consistently with basis fairness, and with the statutory requirement . . . that the order may be issued only after 'due notice and opportunity for hearing.'").

[174] *American Cyanamid*, 606 F.2d at 1312.

[175] *American Cyanamid,* 606 F.2d at 1313.

clarify the Agency's enforcement authority under the accelerated approval regulations, noting that "the most appropriate regulatory approach must be governed by the unique factors of the particular case."[176] This same recognition calls for a hearing in this instance.

2. Substantial Factual Questions Merit a Hearing.

Where the governing regulations call for "subjective and discretionary judgment,"[177] FDA may invoke its summary judgment authority only where it establishes that clinical studies submitted in support of an approval application are "conclusively deficient" in light of applicable regulatory criteria[178] and there are no material issues of fact related to the adequacy of an applicant's submission.[179]

Summary judgment is inappropriate here because the governing regulations are imprecise, and there are ample factual disputes that justify a hearing, including the following issues discussed in greater detail above:

- Whether the data on Avastin and paclitaxel continue to support accelerated approval or are invalidated by data involving Avastin and other chemotherapies
- The basis and likelihood for the hypothesis that there is a differential magnitude of effect when Avastin is used with paclitaxel versus other chemotherapy agents
- Whether the safety profile of Avastin weighs in favor of withdrawal, including specific factual questions identified above regarding how that profile has been characterized in these proceedings
- The balance of benefit to risk for Avastin both based on the available data and as it compares with other agents for MBC
- The extent to which PFS, OS, and other data support other FDA approvals in MBC
- Whether continued accelerated approval—or withdrawal—is consistent with FDA actions in comparable settings

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[176] GAO Report at 61.

[177] *American Cyanamid*, 606 F.2d at 1313.

[178] *Id.* at 1314-15; *see also Hynson*, 412 U.S. at 620 (noting that summary judgment is appropriate where "it is apparent at the threshold that the applicant has not tendered any evidence which on its face meets the statutory standards as particularized by the regulations").

[179] *See Hynson*, 412 U.S. at 620.

- Whether and how FDA is shifting the approval standard for drugs in first-line MBC
- The potential for FDA's actions to inhibit future cancer drug development

These significant issues of fact more than justify a hearing.

In addition, this submission sets forth substantial and important information that FDA has not fully considered to date, the July 2010 ODAC did not have the opportunity to consider, and/or Genentech has not previously had the opportunity to set forth. This new information includes the following:

- An assessment of why the data suggest that the chemotherapy backbone used with Avastin influences the magnitude of the PFS effect
- A statistical evaluation refuting FDA's assertion that the results of E2100 reflect a "random high"
- A comparison of how the benefit–risk profile of Avastin plus paclitaxel relates to that of alternative therapies, such as Gemzar®
- An analysis of how the current data meet the legal and regulatory requirements for accelerated approval, how the current data do not meet the legal and regulatory requirements for withdrawal, and how withdrawal under these circumstances would be inconsistent with FDA precedent
- Analysis and discussion describing the potential adverse implications on drug development of FDA's standards in this case

The leading case of *American Cyanamid Co. v. FDA* is instructive on why a hearing is merited in light of these issues. In that case, FDA issued an NOOH on a veterinary drug, stating that Cyanamid had not submitted adequate and well-controlled tests establishing safe use without veterinarian oversight.[180] After FDA subsequently denied approval without allowing a hearing, Cyanamid appealed to the D.C. Circuit, which ruled that the denial of a hearing was improper.[181]

The D.C. Circuit identified various factual disputes over the meaning of Cyanamid's study data, with Cyanamid interpreting the results of studies in a manner "strikingly different from FDA."[182] Concluding that each of these disagreements constituted

[180] *American Cyanamid*, 606 F.2d at 1309.

[181] *Id.* at 1309, 1323-24.

[182] *Id.* at 1316.

"genuine issue[s] of fact," the D.C. Circuit ruled that FDA's denial of a hearing had been improper:

> Cyanamid presented FDA with scientific studies which in the opinion of some experts proved that Proban may be safely used by dog owners without professional supervision. Cyanamid's experts disputed FDA's interpretation and critique of the studies' results and methods. They raised, too, a number of material questions about the appropriateness of the methodological standards the Director attempted to graft onto the statute. In short, the papers on file in this matter generate several material issues of fact and science that FDA attempted to resolve without a hearing, in contravention of Section 512(c).[183]

In light of these factual disputes, and citing the ambiguity of the applicable regulations ("no particular margin of safety is prescribed by statute or regulation for OTC marketing of animal drugs"),[184] the D.C. Circuit remanded for a hearing on the ground that FDA could not establish that Cyanamid's submissions "conclusively fail[ed]" to demonstrate the product's safety.[185]

A comparable "conflict in responsible expert opinion"[186] and comparable regulatory ambiguity exist here. Genentech has filed considerable data with FDA regarding Avastin, including three adequate and well-controlled studies that establish a statistically significant improvement in PFS. At a minimum, Genentech's disagreement with FDA's stated views regarding the significance of E2100, AVADO, and RIBBON1 creates a number of genuine and substantial issues of material fact that warrant a hearing. The recent recommendation by EMA's CHMP to maintain approval for Avastin's use in combination with paclitaxel, based on the same scientific record before FDA, only highlights the substantial fact issues that exist in this case. As in *American Cyanamid*, these circumstances foreclose summary adjudication.

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[183] *Id.* at 1323.

[184] *Id.* at 1316.

[185] *Id.* at 1319.

[186] *Id.* at 1319.

3. Important Policy Considerations Necessitate a Public Hearing.

As evidenced by the volume of intense and immediate reaction to FDA's proposal, the decision to withdraw Avastin's MBC indication has serious and wide-ranging implications for patients with MBC, their physicians and families, patient advocates, and researchers. These individuals have an interest in Avastin's continued availability for the treatment of MBC, and their interests are entitled to consideration in the context of a hearing.

The public interest is particularly implicated here, because this matter involves the withdrawal of an approved drug and not simply the denial of an initial application for approval. The withdrawal of an existing approval by definition disturbs existing care regimens on which doctors and patients rely. Physicians now have over 2 years of clinical experience treating patients who have seen clinically meaningful benefits as a result of using Avastin for MBC. FDA's decision to withdraw Avastin's MBC indication would derail clinical practice for patients suffering from a disease for which therapeutic options are limited. The serious implications of the Agency's proposal for MBC patients treated with Avastin support a public hearing.

FDA has recognized the substantial public interest in these proceedings with its extensive communications campaign. After issuing the NOOH, FDA held a media call and a stakeholder call,[187] issued a news release,[188] posted questions and answers[189] and a podcast by Dr. Woodcock[190] on its website, and posted notice of

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[187] Transcript, FDA call with stakeholders (16 December 2010); Transcript, FDA media briefing on Avastin (16 December 2010), *available at* http://www.fda.gov/NewsEvents/Newsroom/MediaTranscripts/ucm198091.htm (last visited 14 January 2011)

[188] Press Release, FDA, FDA Begins Process to Remove Breast Cancer Indication from Avastin Label (16 December 2010), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm237172.htm (last visited 14 January 2011).

[189] FDA, Questions and Answers about Avastin (16 December 2010), *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm237095.htm (last visited 14 January 2011).

[190] FDA, Podcast by Dr. Woodcock, M.D., Director, Center for Drug Evaluation and Research, *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ UCM237102.mp3 (last visited 14 January 2011).

the proposal on its Facebook wall[191] and Twitter account.[192] In addition, in an effort to communicate directly with interested parties, Dr. Woodcock issued an open letter to the breast cancer community.[193] FDA's outreach underscores the substantial public interest in these proceedings.

Finally, a public hearing would permit consideration of issues arising from FDA's proposal that have not yet been publicly considered. As an example, the Agency has not yet fully assessed Genentech's proposal to maintain accelerated approval pending the completion of a confirmatory study designed to define further the benefit of Avastin in combination with paclitaxel. Importantly, this proposal offers the dual benefits of (i) maintaining Avastin as a choice for MBC patients and (ii) providing physicians and patients with more data on the benefits of Avastin specifically in combination with weekly paclitaxel.[194] Patients and physicians who have come to rely on Avastin as a treatment option should have an opportunity to understand and comment on this proposal.

CONCLUSION

For the above reasons, Genentech seeks a hearing so that it may present the data on why Avastin plus paclitaxel should retain accelerated approval while Genentech conducts a confirmatory study of this combination.

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[191] http://www.facebook.com/FDA (last visited 14 January 2011).

[192] http://twitter.com/FDA_Drug_Info (last visited 14 January 2011).

[193] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Breast Cancer Community (16 December 2010), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237286.pdf (last visited 14 January 2011).

[194] Physicians have already expressed interest in more data on the benefit of Avastin in combination with paclitaxel and data that could help identify responders. Susan Schaeffer & Stephen Hansen, *Label: no; Access: yes*, BioCentury v. 18 n. 54, A1, A5 (20 December 2010); *see also* Section [III.B] *supra*. For example, Robert Carlson, chair of the NCCN guidelines panel and Professor of Medical Oncology at Stanford University, stated: "One thing I'd like to see is an additional trial of Avastin plus paclitaxel to see if the bigger benefit previously seen is real or not. The second would be a biology marker or gene marker that would allow for selection of patients for Avastin, to protect patients from the toxicity and make the risk-benefit analysis more favorable." Susan Schaeffer & Stephen Hansen, *Label: no; Access: yes*, BioCentury v. 18 n. 54, A1, A5 (20 December 2010).

Respectfully submitted,

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16 January 2011

APPENDIX A
Index of Supportive and Supplementary Documentation Provided in Attachments

Category	Document	Attachment	Citation in Primary Submission Document
Avastin Information	Avastin® USPI (2010)	1	N 72
	Avastin® USPI (2008)	1	N 102; T 8
Avastin Data Source Documents	Avastin® First-Line MBC Integrated Summary of Efficacy (BL125085/191 and 192)	1	N 13, 14, 17, 18, 19, 39, 59, 60, 67; T 8
	Avastin® First-Line MBC Integrated Summary of Safety (BL125085/191 and 192)	1	N 91
Avastin Study Documents	Study E2100 Protocol (Amendment 8; 9 March 2005)	2	N 13
	Study E2100 Protocol (Amendment 9; 22 February 2006)	2	N 13
	Study E2100 Protocol (Amendment 10; 2 May 2007)	2	N 13
	Study E2100 Statistical Analysis Plan (4 April 2007)	2	NA
	Study E2100 Statistical Analysis Plan Supplement (14 May 2007)	2	NA
	Study AVADO (BO17708) Protocol (Amendment G; 20 July 2009)	2	N 13
	Study AVADO (BO17708) Statistical Analysis Plan (31 January 2008)	2	NA
	Study RIBBON1 (AVF3694g) Protocol (Amendment 5; 27 March 2008)	3	N 13
	Study RIBBON1 (AVF3694g) Statistical Analysis Plan (16 April 2008)	3	NA
Avastin Metastatic Breast Cancer Regulatory History	FDA Approval Letter (22 February 2008)	3	NA
	FDA Minutes: Type B (26 February 2009)	3	N 127, 128
	FDA Minutes: Type B (10 January 2006) *(Redaction)*	3	N 62, 63, 65
	Genentech Request for Official Hearing; Docket No. FDA–2010–N–0621 (23 December 2010)	3	NA
Scientific Discussion Papers	Title: Overall Survival in Clinical Studies of First-Line Treatment for Metastatic Breast Cancer	3	N 116, 124
	Title: Response to the Issue Raised by FDA That the E2100 Result May Represent a “Random High”	3	N 50

N = footnote; NA = not applicable (document is not cited in primary submission document); T = table; USPI = United States Package Insert.

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Category	Document	Attachment	Citation in Primary Submission Document
Oncologic Drugs Advisory Committee (ODAC) Materials	20 July 2010 ODAC: Genentech Briefing Book	4	N 75, 87
	20 July 2010 ODAC: Genentech Briefing Book Errata	4	NA
	20 July 2010 ODAC: FDA Briefing Book	4	N 74, 81, 87, 133
	20 July 2010 ODAC: FDA Briefing Book Errata	4	NA
	20 July 2010 ODAC: Genentech Slide Presentation	4	N 85, 89
	20 July 2010 ODAC: FDA Slide Presentation	4	N 81, 103
	20 July 2010 ODAC: Final Minutes	4	N 21, 22
	20 July 2010 ODAC: Transcript	4	N 44, 103, 105, 130, 150, 151, 152, 159, 160, 161
	5 December 2007 ODAC: Genentech Briefing Book	4	N 43
	5 December 2007 ODAC: FDA Briefing Book	4	NA
	5 December 2007 ODAC: Genentech Slide Presentation	4	NA
	5 December 2007 ODAC: FDA Slide Presentation	4	NA
	5 December 2007 ODAC: Final Minutes	4	NA
	5 December 2007 ODAC: Transcript	4	N 40
FDA Materials (16 December 2010)	NOOH Letter to Genentech	5	N 24, 82, 163
	Decision Memorandum	5	N 25, 48, 61, 66, 83, 84, 86, 104, 131, 134
	Letter to Breast Cancer Community	5	N 86, 142, 193
	Press Release	5	N 188
	Question & Answers	5	N189
	Transcript of Janet Woodcock Podcast	5	N 190
	Transcript of Stakeholder Call	5	N 88, 187
	Transcript of Media Call	5	N 90, 187
	FDA Facebook Announcement	5	N 191
	FDA Twitter Announcement	5	N 192

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Category	Document	Attachment	Citation in Primary Submission Document
Other FDA-Related Materials	Transcript of Margaret Hamburg Remarks, Bringing Home the Genome: FDA's Role in Realizing Personalized Medicine	5	N 158
	Federal Register Notice (7 January 2011) Regarding 8 February 2011 ODAC	5	N 101
European Medicines Agency (EMA) Materials	EMA Press Release (16 December 2010)	5	N 26, 92
	EMA Questions & Answers (16 December 2010)	5	N 93
	EMA Guideline on the Evaluation of Anticancer Medicinal Products in Man (15 December 2005)	5	N 113
Treatment Guidelines & Related Documents	NCCN Guidelines for Breast Cancer (Version 1.2011)	5	NA
	NCCN Press Release (29 October 2010)	5	N 94
	ESMO Guidelines Working Group: Primary Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow–Up (Aebi S et al., Ann Oncol 2010:21[Suppl 5]:v9–14)	5	NA
Other Product Information	Abraxane®: USPI (2005)	5	N 102
	Ethyol®: MedImmune Oncology, Briefing Book, 12 March 2003 ODAC	5	N 146, 147
	Ethyol®: Transcript, 8 November 2005 ODAC	5	N 147
	Gemzar®: USPI (2004)	5	N 102
	Gemzar®: FDA Summary Basis of Approval (2004)	6, 7	T 8
	Gemzar®: USPI (Current as of 14 January 2011)	8	N 106
	Gemzar®: Patient Therapy Guide (Current as of 14 January 2011)	8	N 76, 77
	Iressa®: FDA Website, New Labeling and Distribution Program for Gefitinib (Iressa®) (17 June 2005)	8	N 148
	Iressa®: FDA Question & Answer on Iressa® (gefitinib) (17 June 2005)	8	N 148
	Ixempra®: USPI (2007)	8	N 102
	Ixempra®: FDA Summary Basis of Approval (Clinical & Statistical Review) (2007)	8, 9	N 41

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APPENDIX A (cont'd)
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Category	Document	Attachment	Citation in Primary Submission Document
Other Product Information (cont'd)	Ixempra®: USPI (Current as of 14 January 2011)	9	N 109
	Halaven™: USPI (Current as of 14 January 2011)	9	N 102, 125
	Halaven™: FDA Summary Basis of Approval (Summary, Cross-Functional, Clinical & Statistical Review) (2010)	9	N 125
	Herceptin®: USPI (1998)	10	N 102, 105
	Herceptin®: FDA Summary Basis of Approval (1998)	10	NA
	Herceptin®: USPI (Current as of 14 January 2011)	10	N 105
	Mylotarg®: FDA Website, Gematuzumab Ozogamicin (21 June 2010)	10	N 145
	Mylotarg®: FDA Press Release, Gematuzumab Ozogamicin (21 June 2010)	10	N 145
	Taxol®: USPI (Current as of 14 January 2011)	10	N 80
	Taxotere®: USPI (1998)	10	N 102
	Tykerb®: USPI (2007)	10	N 102
	Tykerb®: FDA Summary Basis of Approval (Clinical & Statistical Review) (2007)	11, 12	N 41, 42
Other Supportive Materials	29 February 2008: PFS is a Benefit 'In the Right Context,' Pazdur Says in Q&A on Avastin Approval, The Cancer Letter	12	N 45, 46, 47, 132, 143
	3 March 2008: With Avastin Approval for Breast Cancer, Will More Patients Hit Price Cap?, The Pink Sheet	12	N 132
	16 August 2010: Rob Stein, FDA Considers Revoking Approval of Avastin for Advanced Breast Cancer, The Washington Post	12	N 155
	September 2010: Bevacizumab in Advanced Breast Cancer: FDA Committee Ruling Sparks Response from Oncology Community; Nine Members of the Oncology Community Speak out about Bevacizumab's Role in Metastatic Breast Cancer, The ASCO Post	12	N 97, 108

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APPENDIX A (cont'd)
Index of Supportive and Supplementary Documentation Provided in Attachments

Category	Document	Attachment	Citation in Primary Submission Document
Other Supportive Materials (cont'd)	3 September 2010: Avastin May Trigger Two FDA Decisions: One on Approval, Another on Withdrawal, The Cancer Letter	12	N 136, 156
	October 2010: Avastin Controversy Shakes up Oncology Community, Clinical Oncology News	12	N 85, 98, 99, 137
	1 November 2010: Michael McCaughan Carving REMS out of Oncology? FDA, ASCO Plan Follow-Up Workshop, The RPM Report	12	N 71
	16 December 2010: Amanda Gardner, FDA Advises against Avastin as Treatment for Breast Cancer; but Patients Won't Be Affected for Now, FDA Says, HealthDay News	12	N 154, 157
	16 December 2010: Letter from Dr. Marisa Weiss on Behalf of Breastcancer.org to ODAC members	12	N 114
	16 December 2010: Press Release from American Cancer Society, FDA Begins Process to Remove Indication for Avastin for Metastatic Breast Cancer: Response from Dr. Len Lichtenfeld	12	N 154
	16 December 2010: Press Release from Susan G. Komen for the Cure, Susan G. Komen for the Cure Encourages Continued Coverage for Avastin for Breast Cancer Patients Who Are Benefiting From the Drug	12	N 153
	20 December 2010: Susan Schaeffer & Stephen Hansen, Label: no; access: yes, BioCentury	12	N 96, 194
	6 January 2011: Alicia Mundy, Regulator Defends Avastin Decision; FDA Says Genentech Was Warned of Inadequate Trial Data before Agency Revoked Its Approval for Use in Breast Cancer, The Wall Street Journal Online	12	N 142
	6 January 2011: Andrew Pollack, Medicare Coverage for Breast Cancer Drug Ends in Some States, New York Times Prescription Blog	12	N 144
	7 January 2011: Andrew Pollack, Medicare Contractor Will Pay for Avastin during Appeal, New York Times Prescription Blog	12	N 144

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APPENDIX A (cont'd)
Index of Supportive and Supplementary Documentation Provided in Attachments

Category	Document	Attachment	Citation in Primary Submission Document
References	Albain et al., J Clin Oncol, 2004	13	NA
	Albain et al., J Clin Oncol, 2008	13	T 6
	American Cancer Society, Breast Cancer Facts & Figures 2009–2010	13	N 2, 118
	Bagri et al., Clin Can Res, 2010	13	N 12
	Beslija et al., Ann Oncol, 2009	13	N 4, 5, 7, 79, 115
	Biganzoli et al., J Clin Oncol, 2002	13	T 6
	Bontenbal et al., J Clin Oncol, 2005	13	T 6
	Bowater et al., Cancer Lett, 2008	13	N 121
	Broglio and Berry, J Natl Cancer Inst, 2009	13	N 123
	Brufsky et al., SABCS, 2009	13	N 109
	Burzykowski et al., J Clin Oncol, 2008	13	NA
	Cardoso et al., J Natl Cancer Inst, 2009	13	N 3, 6, 115
	Carey and Sharpless, N Engl J Med, 2011	13	N 125
	Carmichael et al., Proc Am Soc Clin Oncol, 2001	13	T 6
	Chang et al., Cancer, 2003	13	N 5
	Chia et al., Cancer, 2007	13	N 126
	Clinical Study Summary, Study B9E–MA–JHQG, 2008	13	NA
	Giordano et al., Cancer, 2004	13	N 126
	Gligorov and Lotz, Breast Cancer Res Treat, 2008	13	N 3
	Gray et al., J Clin Oncol, 2009	13	N 37, 41
	Hamilton and Hortobagyi, J Clin Oncol, 2005	13	N 10
	Hudis, ASCO 2010, Transcript, MBC Education Session	13	N 78
	Jassem et al., J Clin Oncol, 2001	13	T 6
	Jennison and Turnbull, Chapman & Hall/CRC, 2000	13	N 49
	Lueck et al., Proc Am Soc Clin Oncol, 2006	13	T 6
	Mackey et al., Proc Am Soc Clin Oncol, 2002	13	T 6
	Masuda et al., J Clin Oncol, 2010	13	N 52
	Miles et al., SABCS, 2010	13	N 149

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Category	Document	Attachment	Citation in Primary Submission Document
References (cont'd)	Mackey et al., SABCS, 2009	13	N 52
	Miller et al., N Engl J Med, 2007	13	N 38, 51
	Moulder and Hortobagyi, Clin Pharm Ther, 2008	13	N 3
	Nabholtz et al., J Clin Oncol, 2003	13	T 6
	O'Shaughnessy et al., N Engl J Med, 2011	13	N 125
	Osborne et al., Ann Rev Med, 2011	13	N 9
	Pfizer, Inc., SUN1094 study synopsis, 2010	14	N 53
	Presta et al., Cancer Res, 1997	14	N 11
	Richey et al., J Clin Oncol, 2009	14	N 139
	Rugo et al., J Clin Oncol, 2010	14	N 52
	Saad et al., J Clin Oncol, 2010	14	N 119, 120
	Sargent et al., J Clin Oncol, 2008	14	NA
	Sherrill et al., Br J Cancer, 2008	14	NA
	Slamon et al., Science, 1987	14	N 8
	Slamon et al., Science, 1989	14	N 8
	Slamon et al., N Engl J Med, 2001	14	NA
	Sledge et al., J Clin Oncol, 2003	14	T 6
	Smith et al., Ann Oncol, 2010	14	N 54, 70
	Telli and Carlson, Clin Breast Cancer, 2009	14	N 5, 115
	Therasse et al., J Natl Cancer Inst, 2000	14	N 111
	Verma et al., Oncologist, 2011	14	N 117, 122
	Zielinski et al., J Clin Oncol, 2005	14	T 6

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APPENDIX B
AVADO: Efficacy Results Submitted to FDA prior to E2100 Approval

	Doc+PL (n=241)	Doc+AVF 7.5 (n=248)	Doc+AVF (n=247)
Progression-free survival (final data)			
Stratified HR		0.72	0.64
(95% CI)		(0.56, 0.91)	(0.50, 0.82)
Median, months	8.0	8.7	8.8
p-value		0.0072	0.0003
Overall survival (interim data)			
Deaths, %	21	20	15
Stratified HR (95% CI)		0.97 (0.63, 1.48)	0.65 (0.42, 1.02)
Median, months	NR	NR	NR
Objective response rate [a]			
Objective response rate, %	45	55	64
Between-arm difference, %		10	19

AVF=Avastin 15 mg/kg every 2 weeks; AVF 7.5=Avastin 7.5 mg/kg every 3 weeks; CI=confidence interval; Doc=docetaxel; HR=hazard ratio; NR=not reached; PL=placebo.

[a] Objective response rate was based on patients with measurable disease at baseline.

APPENDIX C
Subgroup Efficacy Analysis for Study MO19391 (ATHENA):[195] Time to Progression in the Patients Who Received Avastin with Weekly Paclitaxel

Total number of patients [a]	2264
Patients treated with weekly paclitaxel	325
Patients with progressive disease	235
Median TTP (95% CI) (months)	10.6 (9.2, 11.8)

CI = confidence interval; TTP = time to disease progression.

Note: Data on file.

[a] Patients who met eligibility criteria and received at least one dose of Avastin.

[195] ATHENA (Avastin THErapy for advaNced breAst cancer) Open-label study of bevacizumab (AVASTIN®) plus taxane monotherapy or in combination for the first-line treatment of patients with locally recurrent or metastatic breast cancer.

APPENDIX D
Avastin Experience in Clinical Trials and the Postmarketing Setting

From the Avastin® (bevacizumab) Investigator Brochure (v.18, November 2010) ("IB").

The overall safety profile of bevacizumab presented in this IB is based on the following sources of information:

- Approximately 17774 patients with advanced cancer from Phase I–Phase IV clinical trials who received bevacizumab either as a single-agent or in addition to chemotherapy or other therapies (139 patients with various cancers in Phase I trials, 3329 patients with metastatic carcinoma of the colon or rectum, 3618 patients with adjuvant colon cancer, 2725 patients with locally advanced or metastatic NSCLC, 2558 patients with locally recurrent or metastatic breast cancer, 2067 patients with ovarian cancer, 879 patients with mRCC, 616 patients with pancreatic cancer, 601 patients with castrate-resistant prostate cancer, 218 patients with glioblastoma).
- An additional 3867 patients from two post-marketing studies in mCRC (AVF2941n and MO18024), 2264 patients from a post-marketing study in mBC (MO19391), and 2212 patients from a post-marketing study in NSCLC (MO19390).
- Standard safety reporting from the use of the marketed product (over 812 000 patients have been exposed to bevacizumab as a marketed product or in clinical trials up until 25 February 2010).

APPENDIX E
Market Share Data for Avastin and Gemzar® (Total Patient Share in 2006–08, New Patient Share in 2009–10)

	2006 Avg	2007 Avg	1H '08 Avg	2H '08 Avg	1H '09 Avg	2H '09 Avg	Q1 '10	Q2 '10	Q3 '10	Q4 '10
Gemzar® + paclitaxel	4%	1%	2%	0.5%	0.1%	0.5%	0.2%	0.5%	0.5%	0.5%
Gemzar® + other	13%	11%	5%	4%	4%	3%	4%	4%	4%	4%
Total Gemzar®	**18%**	**13%**	**7%**	**4%**	**4%**	**3%**	**4%**	**4%**	**5%**	**5%**
Source: IntrinsiQ, LLC										
Paclitaxel single agent without Avastin	3%	4%	4%	5%	5%	7%	7%	8%	5%	10%
Paclitaxel single agent + Avastin	9%	12%	18%	19%	22%	23%	26%	24%	24%	21%
Total paclitaxel single agent (±Avastin)	**13%**	**16%**	**22%**	**23%**	**27%**	**30%**	**33%**	**32%**	**30%**	**31%**
Source: IntrinsiQ, LLC and TNS Healthcare Quarterly Chart Audits commissioned by Genentech (pre-2009); ZS Associates Chart Audits (2009–10)										
Chart Collection Window							Nov 1 '09 to Mar 1 '10	Feb 1 to May 1	May 1 to Aug 30	Jul 15 to Nov 8
Total Avastin	**18%**	**24%**	**33%**	**40%**	**53%**	**54%**	**57%**	**59%**	**50%**	**45%**
Source: TNS Healthcare Quarterly Chart Audits commissioned by Genentech (pre-2009); ZS Associates Chart Audits (2009–10)										
Study								Q3 '10 Wave	Q4 '10 Wave 1	Q4 '10 Wave 2
Use window [a]								Jul 25 to Oct 25	Sep 2 to Dec 2	Sep 20 to Dec 20
Total Avastin								**42%**	**38%**	**35%**
Source: MedPanel LLC Market Research commissioned by Genentech										

Note: Data are for first-line treatment of HER2-negative MBC.

[a] Oncologist-stated use discounted by historical difference between oncologist-stated use and chart audit data.

APPENDIX F
Declarations

Submission of Genentech, Inc.
in Response to the Food and Drug Administration's
Notice of Opportunity for a Hearing and Proposal to Withdraw Approval
of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel
for the First-Line Treatment of Patients with Metastatic Breast Cancer

Docket No. FDA-2010-N-0621

DECLARATION OF SANDRA HORNING, M.D.

1. My name is Sandra J. Horning, M.D. I am the Senior Vice President and Global Head for Clinical Development Hematology/Oncology at Genentech, Inc. ("Genentech"). I have more than 25 years of experience as a practicing oncologist, clinical investigator, and am an Emeritus Faculty of the Stanford University School of Medicine.

2. As a co-signatory of the Submission of Genentech, Inc. in Response to the Food and Drug Administration's Notice of Opportunity for a Hearing and Proposal to Withdraw Approval of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel for the First-Line Treatment of Patients with Metastatic Breast Cancer (the "Submission"), I played a central role in developing the information and analyses set forth in the Submission, which have drawn on the work of various professionals at Genentech. I stand ready to attest to the accuracy of the information and analyses set forth in the Submission as a presenter at the hearing of the U.S. Food and Drug Administration in this matter.

3. In particular, I stand ready to discuss the accuracy of the Avastin clinical efficacy and safety data and the unmet medical need for Avastin in metastatic breast cancer, including as those facts are discussed in the Submission in the Background, Parts II.A, II.B, and II.C, and the accompanying supportive and supplementary documentation provided as attachments and described in Appendix A.

I declare under penalty of perjury that the foregoing is true and correct. Executed on January 14, 2011 at South San Francisco, California.

_____ /s/ Sandra J. Horning, M.D.

Submission of Genentech, Inc.
in Response to the Food and Drug Administration's
Notice of Opportunity for a Hearing and Proposal to Withdraw Approval
of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel
for the First-Line Treatment of Patients with Metastatic Breast Cancer

Docket No. FDA-2010-N-0621

DECLARATION OF BEATRICE LEUNG

4. My name is Beatrice Leung. I am in Pharma Development Regulatory Program Management at Genentech, Inc. ("Genentech").

5. I have overseen the compilation of the supporting and supplementary documentation included as Attachments in the Submission of Genentech, Inc. in Response to the Food and Drug Administration's Notice of Opportunity for a Hearing and Proposal to Withdraw Approval of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel for the First-Line Treatment of Patients with Metastatic Breast Cancer (the "Submission"), with the assistance of personnel in Genentech's Pharma Development Oncology, Pharma Development Biometrics, and Pharma Development Regulatory groups. I attest that the documents included as Attachments and identified in Appendix A of the Submission are true and correct copies of such documents.

I declare under penalty of perjury that the foregoing is true and correct. Executed on January 14, 2011 at South San Francisco, California.

_____ /s/ Beatrice Leung

Submission of Genentech, Inc.
in Response to the Food and Drug Administration's
Notice of Opportunity for a Hearing and Proposal to Withdraw Approval
of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel
for the First-Line Treatment of Patients with Metastatic Breast Cancer

Docket No. FDA-2010-N-0621

DECLARATION OF JAMES REIMANN, Ph.D.

6. My name is James Reimann, Ph.D. I am a Global Head of Oncology Biostatistics at Genentech, Inc. ("Genentech").

7. I have assisted in developing the information and analyses expressed in this Submission of Genentech, Inc. in Response to the Food and Drug Administration's Notice of Opportunity for a Hearing and Proposal to Withdraw Approval of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel for the First-Line Treatment of Patients with Metastatic Breast Cancer (the "Submission"). I stand ready to address at the hearing of the U.S. Food and Drug Administration in this matter the statistical analyses set forth in the Submission, including the discussion in Section III.C and the data presented in Tables and Figure 1 of the Submission.

8. I also stand ready to address the attachments referenced in Appendix A of the Submission under the category Scientific Discussion Papers, which are true and correct copies of these documents.

I declare under penalty of perjury that the foregoing is true and correct. Executed on January 14, 2011 at South San Francisco, California.

_____ /s/ James Reimann, Ph.D

Submission of Genentech, Inc.
in Response to the Food and Drug Administration's
Notice of Opportunity for a Hearing and Proposal to Withdraw Approval
of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel
for the First-Line Treatment of Patients with Metastatic Breast Cancer

Docket No. FDA-2010-N-0621

DECLARATION OF MICHELLE ROHRER, Ph.D.

1. My name is Michelle Rohrer, Ph.D. I am the Vice President for Regulatory Affairs at Genentech, Inc. ("Genentech").

2. I have assisted in developing the information and analyses in the Submission of Genentech, Inc. in Response to the Food and Drug Administration's Notice of Opportunity for a Hearing and Proposal to Withdraw Approval of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel for the First-Line Treatment of Patients with Metastatic Breast Cancer (the "Submission"); and I stand ready to address them as a presenter at the hearing of the U.S. Food and Drug Administration ("FDA") in this matter.

3. In particular, I stand ready to address the regulatory history of Avastin, including the interactions between FDA and Genentech regarding the approval of Avastin for metastatic breast cancer, including as discussed in the Background and Section III.D of this Submission.

4. I also stand ready to address the information described in the attachments referenced in Appendix A of the Submission under the category Avastin Metastatic Breast Cancer Regulatory History, which are true and correct copies of these documents.

I declare under penalty of perjury that the foregoing is true and correct and that this declaration was signed on January 14, 2011 at South San Francisco, California.

_____ /s/ Michelle Rohrer, Ph.D.