

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)  
U.S. Food and Drug Administration

**Summary of Arguments Supporting CDER's  
Proposal to Withdraw Approval of Avastin's  
Indication for the Treatment of Metastatic Breast Cancer**

Docket No. FDA-2010-N-0621

May 13, 2011

## TABLE OF CONTENTS

I.	EXECUTIVE SUMMARY .....	1
II.	QUESTIONS PRESENTED.....	3
III.	LEGAL AND REGULATORY FRAMEWORK.....	5
	A. Overview of the Accelerated Approval Program.....	5
	B. Confirmation of Clinical Benefit .....	7
	C. Withdrawal Standard .....	11
IV.	BASIS FOR ACCELERATED APPROVAL OF AVASTIN FOR MBC .....	13
	A. The E2100 Clinical Trial .....	14
	B. The AVF2119g Clinical Trial.....	17
	C. CDER’s Analysis of the E2100 and AVF2119g Results .....	18
	D. ODAC’s Advice.....	20
	E. CDER’s Approval of the MBC Indication.....	21
V.	BASIS FOR PROPOSAL TO WITHDRAW APPROVAL OF AVASTIN FOR MBC.....	21
	A. The Clinical Benefit of Avastin in MBC Has Not Been Verified.....	21
	1. The AVADO Clinical Trial .....	22
	2. The RIBBON1 Clinical Trial .....	23
	3. CDER’s Analysis of the AVADO & RIBBON1 Results .....	25
	B. Avastin Poses Significant Safety Risks .....	26
	C. The Risk-Benefit Balance in MBC Is Unfavorable .....	30
VI.	CDER’S RESPONSE TO GENENTECH’S ARGUMENTS AGAINST WITHDRAWAL .....	32
	A. Genentech’s Position that FDA Should "Maintain Approval" for Avastin in MBC is Inconsistent With the Regulatory Framework and the Interests of the Public Health .....	32
	B. Genentech’s Hypothesis Regarding Different Chemotherapy Partners Is Not Supported by the Data.....	35
	C. Genentech’s Claim That CDER Has Changed its Approval Standards Is Incorrect.....	40
	D. Genentech’s Efforts to Downplay the Serious Safety Risks Associated With Avastin Are Misleading .....	42
	E. Genentech’s Reliance on Decisions of Other Authorities Is Misplaced.....	44
	F. The New Information That Genentech Cites Does Not Alter the Risk-Benefit Balance of Avastin for MBC .....	52
VII.	CONCLUSION.....	54

## LISTING OF TABLES

Table 1: E2100 Efficacy Results.....	15
Table 2: AVF2119g Efficacy Results .....	17
Table 3: Pooled Analysis of Selected Grade $\geq 3$ Adverse Reactions in Patients Treated in the First-Line Setting: Safety-Evaluable Patients (per Genentech) .....	28
Table 4: Comparison of Adverse Event Collection in E2100, AVADO, and RIBBON1 .....	29
Table 5: Selected Adverse Event in the AVADO Trial by Treatment Arm .....	29

## List of Abbreviations

BLA	Biologics License Application
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-Free Survival
ECOG	Eastern Cooperative Oncology Group
FACT-B	Functional Assessment of Cancer Therapy- Breast
FD&C Act	Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GI	Gastrointestinal
HR	Hazard Ratio
HRQL	Health-Related Quality of Life
IND	Investigational New Drug Application
IRF	Independent Radiology Review Committee
IRRC	Independent Radiology Review Committee
MBC	Metastatic Breast Cancer
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOOH	Notice of Opportunity for a Hearing
ODAC	Oncologic Drugs Advisory Committee
ORR	Overall Response Rate
PFS	Progression-Free Survival
PHS Act	Public Health Service Act
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
STN	Submission Tracking Number
TOI	Trial Outcome Index
TTP	Time to Progression
VEGF	Vascular Endothelial Growth Factor

The Center for Drug Evaluation and Research (CDER or the Center) of the Food and Drug Administration (FDA or the Agency) hereby submits its summary of arguments in support of the proposed withdrawal of approval for Avastin's metastatic breast cancer indication, pursuant to the February 23, 2011, instructions of Dr. Karen Midthun, Presiding Officer for the June 28-29, 2011 hearing.

## **I. EXECUTIVE SUMMARY**

CDER approved the use of Avastin (bevacizumab) for first-line treatment of metastatic breast cancer (MBC) in February 2008, under the Agency's accelerated approval program. Avastin is approved for use in combination with the chemotherapy drug, paclitaxel, for the treatment of patients who have not previously received chemotherapy for metastatic HER2-negative breast cancer (the MBC indication). Accelerated approval was based on data showing an increase in a clinical outcome measure called progression-free survival (PFS) in a single, open-label clinical trial. PFS is the time from initiation of therapy (often defined in clinical trials as the time from randomization) until measurable growth of tumor(s) or death from any cause. PFS does not necessarily correspond to how a patient feels or how long a patient will survive. Instead, it is based primarily on radiographic measurement of tumor growth.

CDER took the unprecedented step of granting accelerated approval to Avastin for MBC based solely on an interim analysis of its treatment effect on PFS in one clinical trial, known as E2100. This was the first approval of a non-hormonal agent in which evidence of a treatment effect on PFS alone was viewed not as a surrogate endpoint, but rather as a clinical benefit because of the magnitude of the improvement in PFS. The E2100 trial did not demonstrate that Avastin helped patients live longer or that it improved their quality of life. A second trial of

Avastin in MBC patients failed to support the findings of E2100 in later stage disease.<sup>1</sup> For these reasons, the terms of the accelerated approval of Avastin for MBC required Genentech to conduct additional trials to verify the clinical benefit of the product.

The data from the E2100 trial showed a 5.5-month improvement in median PFS. CDER granted accelerated approval based on this data, because, in its best scientific judgment at that time, the magnitude of PFS in the single trial suggested that Avastin held promise for patients with MBC — a serious and life-threatening disease. Unfortunately, the promise of Avastin’s MBC indication has not been fulfilled. The required post-approval trials, which were proposed by Genentech and agreed to by CDER, have failed to confirm the magnitude of effect on PFS that was seen in the trial supporting approval. Instead, they showed increases in median PFS ranging from under one month to 2.9 months — well short of the 5.5-month improvement in median PFS observed in the E2100 trial.<sup>2</sup> All trials showed serious safety risks associated with the use of Avastin. Based on these data and the results of two additional trials that Genentech has submitted to CDER, there is no evidence that Avastin improves overall survival or quality of life in MBC patients.

Balanced against Avastin’s minimal benefits in MBC (smaller-than-expected effect on PFS and no effect on overall survival) are the increased risks of serious safety problems resulting from its use, including congestive heart failure, stroke, hypertension, gastrointestinal perforation, fistula formation, proteinuria, and hemorrhage. All clinical trials show an overall increase in

---

<sup>1</sup> In this second trial, known as AVF2119g, there was no statistically significant difference in PFS between the treatment arms [HR 0.98 (95% CI 0.77, 1.25) p=0.86]. The median PFS was 4.2 months in the chemotherapy alone arm and 4.9 months in the chemotherapy plus Avastin arm.

<sup>2</sup> In the E2100 trial, median PFS in the Avastin/paclitaxel combination arm was 11.3 compared to 5.8 months over the paclitaxel alone arm (p<0.0001, Hazard Ratio (HR) 0.48,0.39,0.61). In the post-approval trials, median PFS was between .9 and 2.9 months, with hazard ratios ranging from 0.62 to 0.69, favoring the Avastin plus paclitaxel arm for all studies.

serious and life-threatening adverse reactions or deaths associated with the use of Avastin when compared to the use of chemotherapy alone, with the original trial supporting accelerated approval of Avastin showing an absolute increase of more than 20%. Deaths attributed to Avastin were observed in approximately 0.8 to 1.7% of the breast cancer patients enrolled in the trials.

The post-approval studies that Genentech submitted to CDER have failed to verify the drug's clinical benefit in the MBC indication. The limited effectiveness of Avastin for MBC, balanced against the risks of serious and life-threatening adverse reactions or death, lead to an unfavorable risk-benefit profile for this product. If CDER had had access to these data in 2008, it would not have granted either accelerated approval or "regular approval" for the use of Avastin to treat MBC. Accordingly, in the interest of the public health, approval of the MBC indication should be withdrawn.

## **II. QUESTIONS PRESENTED**

The Notice of Hearing published on May 11, 2011 (76 Fed. Reg. 27332) presents 3 questions to be resolved at the hearing, to which CDER responds as follows:

***Question No. 1: Do the AVADO and RIBBON1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved?***

***Response: Yes.*** The AVADO and RIBBON1 trials failed to substantiate the magnitude of PFS that was seen in the E2100 trial. Because the data on Avastin show no improvement in overall survival or quality of life for MBC patients, CDER requires that the effect of the product on PFS must be substantial – of the same or similar magnitude as the 5.5 month improvement shown in the E2100 trial – to constitute the "clinical benefit" required under the accelerated approval regulations. The confirmatory trials showed that Avastin had a small effect on PFS in MBC patients. Absent an effect on overall survival or improved quality of life, the minimal

effect on PFS is not enough to verify that Avastin provides clinical benefit in the MBC indication in view of Avastin's serious side effects, including death. Accordingly, the grounds for withdrawal of approval under 21 CFR 601.43(a)(1) are met.

***Question No. 2:*** (a) *Does the available evidence demonstrate that Avastin has not been shown to be effective for the breast cancer indication for which it was approved?* (b) *Does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved, in that Avastin has not been shown to present a clinical benefit that justifies the risks associated with use of the product for this indication?*

***Response:*** *Yes.* The totality of the available evidence demonstrates that the drug is not shown to be safe and effective for the MBC indication. Four out of the five studies that Genentech submitted to CDER showed no effect or minimal effect on PFS, and none of the studies showed that Avastin improved overall survival or quality of life. All trials showed an increased risk of serious side effects. The grounds for withdrawal of approval under 21 CFR 601.43(a)(6) are therefore also met.

***Question No. 3:*** *If the Commissioner agrees with the grounds for withdrawal set out in issue 1, issue 2.A, or issue 2.B, should FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit?*

***Response:*** *No.* The statute and regulations provide that accelerated approval may be withdrawn when post-approval studies fail to verify clinical benefit or when the evidence establishes that the drug is not safe and effective for its approved indication. CDER has conducted extensive analyses of all available data and has made a scientific judgment that the evidence simply does not justify keeping the product on the market for this indication in light of the serious adverse events attributable to the drug. Permitting Avastin to remain on the market for the MBC indication while Genentech designs and conducts additional studies would not be in

the interest of the public health and would jeopardize the integrity of the accelerated approval program.

### **III. LEGAL AND REGULATORY FRAMEWORK**

#### **A. Overview of the Accelerated Approval Program**

The accelerated approval framework was created in 1992 to expedite the approval of promising new therapies for serious and life-threatening illnesses, such as HIV/AIDS and cancer.<sup>3</sup> The program is intended to strike a balance between making treatments available to patients at the earliest possible time and the need for further study of the drug or biological product to verify its clinical effects.

Accelerated approval is available only for drugs and biological products that treat serious or life-threatening diseases and only where the new product appears to provide a meaningful therapeutic benefit over existing therapy.<sup>4</sup> Under the terms of the accelerated approval regulations, CDER may grant accelerated approval for a new drug or biologic based on adequate and well controlled clinical trials establishing that the product (1) has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or (2) has an effect on a clinical

---

<sup>3</sup> FDA proposed the accelerated approval regulations in April 1992 and adopted them in December 1992. 57 Fed. Reg. 13234 (Apr. 15, 1992); 57 Fed. Reg. 53942 (Dec. 11, 1992). Refer to Appendix 1 for the April 15, 1992, *Federal Register* document. Refer to Appendix 2 for the December 11, 1992, *Federal Register* document. FDA promulgated these regulations under section 351 of the Public Health Service Act (PHS Act) and sections 505 and 701 of the Food, Drug, and Cosmetic Act (FD&C Act or the Act). The Agency's authority to act under the accelerated approval program was made explicit in the Food and Drug Administration Modernization Act of 1997 (FDAMA), Public Law 105-115, which added section 506 to the FD&C Act. The legislative history of FDAMA indicates that Congress intended to codify, without change, FDA's accelerated approval regulations. See, e.g., House of Representatives Report 105-310, p. 55, "New FDCA subsection 741(b) [now section 506(b)] provides an alternative basis for approving fast track products that essentially codifies FDA's accelerated approval regulation." Copy provided as Appendix 3.

<sup>4</sup> The Agency has stated that it intends "to interpret existing treatment under the accelerated approval regulations to mean, in the context of approval based on a surrogate, a treatment that has demonstrated a clinical benefit under conventional approval standards (21 CFR 314.105, 314.125, 601.2)." FDA draft guidance for industry, *Available Therapy* (July 2004) at 5. Refer to Appendix 4 for a copy of this guidance.

endpoint other than survival or irreversible morbidity. In either case, the applicant must “study the . . . 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.”<sup>5</sup> Products approved under these regulations are subject to the expedited withdrawal provisions of §601.43. Applicants who object to these provisions may seek regular approval rather than accelerated approval.

More than 100 indications for drugs and biologics have received accelerated approval since the inception of the program. The program has allowed for earlier approval of many new treatment options for patients with serious or life-threatening illnesses, in some cases years before the drug would have been available under regular approval procedures. In a small percentage of cases, confirmatory studies of oncology products or indications have failed to demonstrate clinical benefit, and such products and indications have been withdrawn. Overall, the program has been a success, particularly for patients with HIV/AIDS and cancer, for whom accelerated approval of promising drugs has dramatically expanded the early availability of effective treatment options and has improved both quality of life and survival.

The accelerated approval program is not intended to change the approval standard for drugs and biologics. Rather, it is rooted in the fundamental regulatory requirement that a product must be safe and effective as a condition of marketing approval in the United States. The Agency expects that the “evidence *available at the time of approval* . . . will meet the statutory standard [for approval], in that there must be evidence from adequate and well-controlled studies

---

<sup>5</sup> 21 CFR 601.41. Regulations have been established for the accelerated approval of drugs approved under new drug applications (NDAs) (21 CFR part 314, subpart H) and biological products approved under biologic license applications (BLAs) (21 CFR part 601, subpart E). Because Avastin is a biological product approved under a BLA, the part 601 regulations are cited in this document. Throughout this document, references to *drugs* include both human drugs and biological products unless otherwise specified.

showing that the drug will have the effect it is purported to have . . . .”<sup>6</sup> Accelerated approval is dependent on compliance with certain post-approval requirements, including the timely completion of studies to verify and describe the expected clinical benefit. If post-approval clinical trials fail to verify clinical benefit, or if “[o]ther evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use,” the Agency may withdraw approval. 21 CFR 601.43(a)(1) and (a)(6). As the Agency explained during the rulemaking process, it must be able to withdraw approval when clinical benefit is not confirmed, because “[o]therwise, the risk of continued exposure of patients with serious or life-threatening diseases to ineffective or unsafe drugs outweighs the potential benefits.”<sup>7</sup>

For a small percentage of accelerated approval indications, clinical benefit will not be verified, and the indication will be withdrawn. This is the trade-off for early availability of promising drugs for severe and life-threatening diseases. If the Agency were unable to withdraw marketing approval when post-approval studies fail to verify clinical benefit, the success of the accelerated approval program would be jeopardized.

## **B. Confirmation of Clinical Benefit**

In the context of the accelerated approval program, CDER considers *clinical benefit* to mean that treatment with the drug prolongs the lives of patients or improves how patients feel or

---

<sup>6</sup> Section 505(d) of the FD&C Act (21 U.S.C. 355(d)) contains a “substantial evidence” standard, which means “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling . . . .” The accelerated approval program is designed to approve products consistent with this standard, but based on different types of data at the time of approval. Final Rule, 57 Fed. Reg. 58942, 58943-44 (Dec. 11, 1992). See Appendix 2.

<sup>7</sup> New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, Proposed Rule, 57 Fed. Reg. 13234, 13239 (Apr. 15, 1992). See Appendix 1.

function. In the oncology setting, and particularly in the case of incurable cancers such as MBC, clinical benefit generally means prolonging patients' lives and/or improving the quality of their lives. Only when the risk-benefit balance is favorable does a treatment provide clinical benefit.

Approval of certain oncology indications, such as the approval of Avastin for MBC, may be based on the endpoint of PFS. As stated above, PFS is the time from initiation of therapy (often defined in clinical trials as the time from randomization) until measurable growth of tumor(s) and/or death from any cause. PFS is primarily evaluated by radiographic measurement of tumor growth. Because radiographic changes may not directly affect how a patient feels or functions, an improvement in PFS must be robust and of sufficient magnitude to demonstrate a favorable risk-benefit balance in relation to observed adverse events, disease setting, and available therapies. As FDA has explained in guidance:

Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies.<sup>8</sup>

A positive effect on a *clinical endpoint* (which generally means an event, outcome, or sign measured in patients to determine whether an intervention being studied is beneficial) is not necessarily tantamount to a finding of net *clinical benefit*. A trial may show that a drug has a statistically significant effect on a clinical endpoint — like PFS — without providing a meaningful clinical benefit to the patients. To determine whether the drug provides clinical benefit, the magnitude of effect on a clinical endpoint must be viewed in the context of the drug's safety risks and its impact on patients' quality and quantity of life.

---

<sup>8</sup> FDA guidance for industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007) at 8. See Appendix 5.

A trial intended to detect effects on PFS must be designed to evaluate and minimize potential bias or uncertainty in tumor endpoint assessments. When tumor measurement-based endpoints are the sole evidence of efficacy in a single trial, confirmatory evidence from a second trial may be needed. In addition, when PFS is the primary clinical endpoint, tumor assessments generally should be verified by central reviewers blinded to trial treatments. This measure is especially important when the trial itself is not blinded. Finally, missing data can complicate analysis of PFS. An imbalance in the proportion of patients lost to follow-up can bias the PFS measurement by overestimating PFS in the treatment arm with less follow-up.

The confirmatory trials for oncology products that are used in combination with chemotherapy agents do not necessarily match the exact indication for which accelerated approval was granted. In the case of Avastin, for example, the two confirmatory trials that Genentech submitted to CDER evaluated Avastin in combination with chemotherapy drugs other than paclitaxel, the chemotherapy partner for which accelerated approval was granted. This approach stems in part from practical considerations. It would be difficult to enroll patients in a blinded clinical trial involving an approved indication because they would prefer to obtain such treatment outside of the controlled trial and not risk being assigned to the placebo or control arm. For accelerated approvals in oncology, CDER has encouraged the conduct of post-approval studies performed in different conditions (for example, in combination with one or more chemotherapy agents, at different doses, on different schedules, or in different stages of disease). This approach may further characterize the risks and benefits of the drug while allowing the applicant to obtain expanded indications for the drug and fulfilling the post-approval requirement to confirm clinical benefit under accelerated approval.

In the case of Avastin for the treatment of MBC, where the initial trial showed an

improvement in median PFS of 5.5 months, CDER expected Genentech to verify the magnitude of PFS, through additional trial results, and to provide additional information on overall survival. This was intended to verify that PFS of a substantial magnitude could be observed consistently and that overall survival was not negatively affected. Genentech's postmarketing trials, however, showed a magnitude of PFS significantly lower than seen in the initial trial (PFS in the subsequent trials in nearly 2,000 patients ranged from 0.9 months to 2.9 months). The studies also showed no evidence that Avastin improves overall survival or health-related quality of life (HRQL) for MBC patients.<sup>9</sup> HRQL data from patient reported outcomes were collected in three of five Avastin MBC trials submitted to CDER, and none of these data showed a reliable effect, perhaps in part because of the large amount of missing data. When these data are balanced with the serious risks associated with Avastin (including cardiac failure, perforations, hemorrhage, and death), clinical benefit is absent and therefore has not been confirmed or verified, as required for accelerated approval products.

CDER has proposed to withdraw Avastin's MBC indication because: (1) the confirmatory trials failed to verify clinical benefit and (2) Avastin for MBC has an unfavorable risk-benefit balance (serious safety risks with no or limited effectiveness). In order for the accelerated approval system to serve its purpose and not operate as a lower approval standard, CDER must be able to withdraw approvals when it determines, based upon careful consideration of the data, that the confirmatory trials have failed to verify clinical benefit.

---

<sup>9</sup> FDA defines health-related quality of life (HRQL) as "a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life." Claiming a statistical and meaningful improvement in HRQL implies: (1) that all HRQL domains that are important to interpreting change in how the clinical trial's population feels or functions as a result of the targeted disease and its treatment were measured; (2) that a general improvement was demonstrated; and (3) that no decrement was demonstrated in any domain. Guidance for industry, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (Dec. 2009) at 32. See Appendix 35.

### C. Withdrawal Standard

FDA regulations provide for the accelerated withdrawal of approval if “a postmarketing clinical study fails to verify clinical benefit” or “[o]ther evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.”<sup>10</sup> The withdrawal process was intended to be “streamlined” and “expeditious”<sup>11</sup> while still providing “a fair opportunity for presentation of views.”<sup>12</sup> The Agency has emphasized that “as part of the approval process under this rule, applicants will have agreed that these withdrawal procedures apply to the drug for which they seek approval; applicants objecting to these procedures may forego approval under these regulations and seek approval under the traditional approval process.”<sup>13</sup>

Inherent in the accelerated approval process is a risk-benefit analysis of the product. Neither the statutes that govern the accelerated approval program – the Public Health Service Act (PHS Act) and the Federal Food, Drug, and Cosmetic Act (FD&C Act) – nor the accelerated approval regulations refer to particular endpoints. The safety standard reflected in both the FD&C Act and the PHS Act – that a drug must be shown to be safe for its intended use – involves a risk-benefit judgment. Any clinical effect shown must be such as to outweigh the risks of the treatment under the conditions of use. Approval under the accelerated approval process requires, therefore, that “the effect shown be, in the judgment of the Agency, clinically

---

<sup>10</sup> 21 CFR 601.43(a)(1), 601.43(a)(6). The PHS Act, which, along with the FD&C Act, governs biological products, does not specify license revocation procedures, except to state that licenses would be suspended and revoked “as prescribed by regulations.” 42 U.S.C. 262(d)(1). Under section 506 of the FD&C Act, the Agency may call for expedited withdrawal if, among other things, “a post-approval study . . . fails to verify clinical benefit of the product,” or “other evidence demonstrates that the . . . product [approved under the accelerated approval regulations] is not safe or effective under the conditions of use” (section 506(b)(3)(B-C) of the FD&C Act).

<sup>11</sup> H.R. Rep. 105-310 at 55. See Appendix 3.

<sup>12</sup> 57 Fed. Reg. at 13238 (April 15, 1992). See Appendix 1.

<sup>13</sup> 57 Fed. Reg. at 58944. See Appendix 2.

meaningful, and of such importance as to outweigh the risks of treatment.”<sup>14</sup> In the preamble to the final rule, FDA stated that “[s]hould well-designed post-approval studies fail to demonstrate the expected clinical benefit, the benefit expected at the time of approval (reasonably likely to exist) would no longer be expected and the totality of the data, showing no clinical benefit, would no longer support approval.”<sup>15</sup>

Without a demonstration of clinical benefit, “the risk-benefit analysis [of an accelerated approval product] changes significantly. . . .”<sup>16</sup> The continued marketing of the drug to treat patients with a serious or life threatening disease under those circumstances “is inappropriate and marketing approval should be rapidly withdrawn” under the “streamlined, expeditious procedure” in 21 CFR 601.43.<sup>17</sup> In other words, “accelerated withdrawal” is an integral part of the accelerated approval framework. Once post-approval trials fail to demonstrate the expected clinical benefit, the accelerated approval rubric does not contemplate – as Genentech argues – that the Agency should “maintain” approval while an applicant designs and conducts more trials with the hope of eventually verifying clinical benefit. If CDER were forced to allow products to stay on the market when the risk-benefit analysis shows that the product is not safe and effective for its intended use, the accelerated approval program would be significantly undermined.

---

<sup>14</sup> *Id.*

<sup>15</sup> *Id.*

<sup>16</sup> 57 Fed. Reg. at 13238 (April 15, 1992). See Appendix 1.

<sup>17</sup> *Id.*

#### IV. BASIS FOR ACCELERATED APPROVAL OF AVASTIN FOR MBC

Avastin is a monoclonal antibody product that is used in combination with chemotherapy to treat various types of cancer.<sup>18</sup> CDER first approved Avastin in February 2004 for the treatment of colon cancer.<sup>19</sup> CDER granted accelerated approval of Avastin for the treatment of metastatic breast cancer in February 2008, based on the promising results of the E2100 trial.

The metastatic breast cancer (MBC) indication for Avastin is described in the product's approved labeling:

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

The effectiveness of Avastin in MBC is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.

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

See appendix 34, FDA-approved label for Avastin (INDICATIONS AND USAGE).

---

<sup>18</sup> Avastin is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. It is approved for the treatment of (1) First-line metastatic carcinoma of the colon and rectum in combination with intravenous 5-fluorouracil-based chemotherapy (February 26, 2004); (2) Second-line metastatic color-rectal cancer in combination with oxaliplatin and 5-FU-based chemotherapy (June 20, 2006); (3) First-line metastatic non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel (October 11, 2006); (4) First-line metastatic HER2-negative breast cancer in combination with paclitaxel (accelerated approval, February 22, 2008); (5) Glioblastoma multiforme, as a single agent (monotherapy) for patients with progressive disease following prior therapy (accelerated approval, May 5, 2009); and (6) First-line advanced renal cell carcinoma in combination with interferon alpha (July 31, 2009).

<sup>19</sup> The February 2004 original approval letter is included as Appendix 6.

The accelerated approval of the MBC indication for Avastin was based on the results of two clinical trials: E2100 and AVF2119g.<sup>20</sup> Of these two trials, Avastin had positive efficacy results only in the E2100 trial.<sup>21</sup>

#### **A. The E2100 Clinical Trial**

The E2100 trial, an open-label, randomized multi-center trial comparing paclitaxel to the combination of paclitaxel plus Avastin, enrolled 722 patients with recurrent or metastatic HER2-negative breast cancer who had not received prior chemotherapy for metastatic disease. As described in the revised statistical analysis plan, dated April 4, 2007, the primary endpoint supporting regulatory approval was PFS, with objective response rate (ORR)<sup>22</sup> and overall survival<sup>23</sup> as secondary endpoints. PFS was evaluated retrospectively by an independent radiology review facility (IRF) masked to treatment assignment because of the subjective nature of the PFS endpoint. The IRF analysis supported the investigator-determined PFS results, demonstrating a statistically significant PFS improvement with the addition of Avastin to paclitaxel compared to paclitaxel alone. The median PFS, as determined by the IRF, in the combination arm was 11.3 months compared to 5.8 months in the paclitaxel-alone arm, for an

---

<sup>20</sup> A third trial, AVF0776g, a 75-patient, phase 1-2 study of single-agent therapy in patients with recurrent/progression MBC, was conducted to evaluate the safety and tolerability of Avastin. This study provided evidence of very modest antitumor activity in the form of objective tumor responses. A complete summary of CDER's review is attached at Appendix 7.

<sup>21</sup> See Appendix 7 for a Regulatory History of Avastin's MBC Indication.

<sup>22</sup> ORR is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. Response duration usually is measured from the time of initial response until documented tumor progression. Generally, the FDA has defined ORR as the sum of partial responses plus complete responses. Guidance for industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007), p. 7, copy attached as Appendix 5.

<sup>23</sup> Overall survival (OS) is defined as the time from randomization until death from any cause. The trial period commenced on December 21, 2001 with a data cutoff date of October 21, 2006 for overall survival (approximately 58 months).

increase in median PFS time of 5.5 months [HR 0.48, (95% CI: 0.39, 0.61)] for Avastin plus paclitaxel compared to paclitaxel alone.

There was no statistically significant difference in overall survival [HR, 0.87 (95% CI: 0.72, 1.05), p=0.14].<sup>24</sup> The median survival time was 26.5 months (95% CI: 23.7, 29.2) for the combination versus 24.8 months (95% CI: 21.4, 27.4) for paclitaxel alone. A statistically significant improvement in ORR was also noted; 48.9 versus 22.2 % (p<0.001) of patients experienced responses in the Avastin plus paclitaxel arm compared to paclitaxel alone. All responses were partial responses (meaning tumors were smaller but still present). Efficacy results are summarized below:

**Table 1: E2100 Efficacy Results**

	<b>Paclitaxel N = 354</b>	<b>Avastin + Paclitaxel N = 368</b>
<b>Progression-Free Survival</b>		
# PFS events (%)	184 (51.9%)	173 (47.0%)
Median (month)	5.8 months	11.3 months
HR <sup>1</sup> (95% CI)	0.48 (0.39, 0.61)	
p-value (stratified log-rank)	< 0.0001	
<b>Overall Survival</b>		
# Deaths (%)	238 (67.2%)	243 (66.0%)
Median (month)	24.8	26.5
HR (95% CI)	0.87 (0.72, 1.05)	
p-value (log rank)	0.14	
<b>Objective Response</b>		
# pts w/ meas disease	243	229
Objective response rate (%)	22.2 %	48.9%
Difference in ORR <sup>2</sup>	26.7%	
p-value	< 0.001	

<sup>1</sup> hazard ratio    <sup>2</sup> objective response rate

<sup>24</sup> There was no evidence in the E2100 trial that Avastin improved health-related quality of life (HRQL). HRQL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) Questionnaire and the Trial Outcome Index (TOI). There was a high proportion of missing HRQL data at baseline, and the data differ by more than 10 percent between arms. In addition, patients with missing scores following disease progression or death were assigned 0, the lowest score. If HRQL scores were missing for any reason other than disease progression or death, they were not imputed, and the patient was not included in the analysis. Only 572 patients were included in the analysis for change from baseline at week 17 in TOI due to missing values. This design biases the results toward the arm with more disease progression events, i.e., the control arm.

Collection of adverse reactions was limited in the E2100 trial to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0<sup>25</sup> grade 3-5 adverse events in either study arm and serious adverse events occurring only in the Avastin-containing arm. The addition of Avastin to paclitaxel led to a 20.2% absolute increase in the incidence of grade 3-5 adverse reactions when compared to paclitaxel alone. The increase in the risk of adverse reactions was observed across all major organ systems: neurologic, cardiovascular, constitutional, gastrointestinal, infectious, renal, metabolic, pulmonary, hepatic, skin, musculoskeletal, and bleeding. In contrast, only venous thromboembolic events occurred more frequently with paclitaxel alone (4.3% versus 2.5%). A total of 142 patients (19.6%) discontinued therapy due to adverse reactions, 70 (20%) in the paclitaxel-alone arm and 72 (19.8%) in the paclitaxel plus Avastin arm. Death attributed to protocol treatment was higher in the Avastin plus paclitaxel arm than in the paclitaxel-alone arm (3.0% versus 2.0%); deaths attributed to Avastin in the Avastin plus paclitaxel arm were 1.7%. Causes of death were gastrointestinal perforation (2), myocardial infarction (2), and diarrhea/abdominal pain/weakness/hypotension (2).

The specific adverse event(s) leading to treatment discontinuation were not collected in the E2100 trial. The most common adverse reactions temporally associated with treatment discontinuation in the paclitaxel arm were neuropathy (60%) and allergic reactions (5.7%). Common adverse reactions resulting in treatment discontinuation in the paclitaxel plus Avastin arm based on temporal association were: neuropathy (25%), thrombosis (12.5%), proteinuria (9.7%), hypertension (6.0%), arterial thromboembolic event (5.6%), left ventricular dysfunction (5.6%), and fatigue (5.6%).

---

<sup>25</sup> See Appendix 8 for CTC Version 2.0.

## B. The AVF2119g Clinical Trial

The AVF2119g trial was an open-label, multicenter, randomized trial evaluating Avastin in combination with capecitabine compared with capecitabine alone in 462 patients who had previously received a taxane and anthracycline for breast cancer. The primary endpoint was PFS as determined by an independent review committee. There was no statistically significant difference in PFS between the treatment arms [HR 0.98 (95% CI 0.77, 1.25) p=0.86]. The median PFS was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm. There also was no statistically significant difference in overall survival, which was a secondary endpoint [HR 1.05 (95% CI 0.86, 1.30) p= 0.63, log-rank test]. The median overall survival was 14.5 months in the capecitabine arm and 15.1 months in the capecitabine plus Avastin arm. The ORR was higher with Avastin plus chemotherapy as compared to chemotherapy alone (19.8% versus 9.1%). The efficacy results are summarized below.

**Table 2: AVF2119g Efficacy Results**

	<b>Capecitabine N = 230</b>	<b>Avastin + Capecitabine N = 232</b>
<b>Progression-Free Survival</b>		
# PFS events (%)	126 (54.8%)	146 (62.9%)
Median (month)	4.17	4.86
HR (95% CI)	0.98 (0.77, 1.25)	
p-value (stratified log-rank)	0.857	
<b>Overall Survival</b>		
# Deaths (%)	177 (77.0%)	181 (78.0%)
Median (month)	13.8	13.6
HR (95% CI)	1.05 (0.86, 1.30)	
p-value (log rank)	0.63	
<b>Overall Response</b>		
Overall response rate (%)	21 (9.1%)	46 (19.8%)
Difference in ORR	10.7%	
p-value	0.0011	

All adverse events occurring in AVF2119g were recorded and coded in accordance with NCI CTC (version 2.0). The addition of Avastin to capecitabine resulted in a greater than 14% absolute increase in the incidence of grade 3-4 adverse reactions, mainly due to hypertension, thromboembolism, and other adverse reactions known to be associated with Avastin. The most common adverse reactions observed in the trial (all grades) occurred at a higher rate in the Avastin arm over the control arm. These included bleeding (29.7% versus 12.2%), hypertension (25.3% versus 2.8%) and proteinuria (22.7% versus 8.4%). There were more dose interruptions (65% versus 55%) and dose reductions (79% vs. 65%) reported in the Avastin plus capecitabine arm than in the capecitabine alone arm.

### **C. CDER's Analysis of the E2100 and AVF2119g Results**

CDER had concerns about approving the MBC indication for several reasons. First, the positive effect on PFS was observed in a only single trial and was not accompanied by an improvement in overall survival. Second, this positive trial had shortcomings in design and conduct. For example, there was substantial loss-to-follow-up prior to confirmation of the treatment effect on PFS by an independent group masked to treatment assignment. The lack of effect on overall survival also raised questions about the reliability of the reported magnitude of effect on PFS and raised the possibility that the treatment effect on PFS in the E2100 trial had been overestimated.

Moreover, the addition of Avastin to paclitaxel or to capecitabine exposed MBC patients to additional risks, beyond those associated with the chemotherapy drugs alone. As detailed above, both trials showed that the number of adverse reactions increased with the addition of Avastin to chemotherapy. There was a 20% higher incidence of grade 3-5 toxicity in the E2100 trial, including unique toxicities attributed to Avastin, and a 1.7% Avastin treatment-related

death rate in the Avastin plus paclitaxel arm. A higher incidence of grade 3-4 adverse reactions was reported when Avastin was added to capecitabine. CDER was therefore uncertain about whether the risks of treatment would outweigh the benefits of Avastin in MBC.

CDER's uncertainty was exacerbated by Avastin's lack of effect on PFS in the AVF2119g trial. Although that trial was conducted in a more heavily pre-treated patient population, CDER was concerned that it might more accurately reflect the treatment effect of Avastin in metastatic HER2-negative breast cancer (i.e., that E2100 overestimated the PFS effect), or that differential efficacy could be explained by specific drug interactions with capecitabine; however, no such interactions have been identified in population pharmacokinetic analyses.

Genentech argues that the data from the AVF2119g trial do not negate the findings of E2100 because AVF2119g was conducted in "refractory MBC defined by pre-treatment with anthracyclines and taxanes."<sup>26</sup> In CDER's view, however, the data from AVF2119g are clearly relevant to Avastin's risk-benefit analysis in MBC. These data were submitted by Genentech as part of the supplemental BLA requesting accelerated approval of the first-line MBC indication. In addition, it is not uncommon for evidence from one oncology trial to support an efficacy supplement for treatment of a different stage of the same cancer.<sup>27</sup> CDER recognizes that more heavily pre-treated patients can be less responsive to chemotherapy than those who have not been previously treated. CDER interpreted the AVF2119g trial results with this understanding and concluded that the significant differences in apparent treatment effect in the E2100 trial vs.

---

<sup>26</sup> Genentech response to NOOH, January 16, 2011, Submission at 19 n.36. See Appendix 9 for a copy of the response.

<sup>27</sup> Guidance for industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007), page 3. (Appendix 5)

the AVF2119g trial were not fully accounted for by the extent of prior treatment of the two trial populations.

#### **D. ODAC's Advice**

Given these concerns, CDER sought the advice of the Oncologic Drugs Advisory Committee (ODAC). CDER asked whether an improvement in PFS of a substantial magnitude could be considered a direct measure of clinical benefit and, if so, whether the treatment effect reported by the applicant for E2100 could be considered a direct measure of clinical benefit. The ODAC was convened on December 5, 2007, to discuss these issues.<sup>28</sup> Some members of the committee expressed strong support for the notion that prolongation of PFS was a direct benefit. In these discussions, a delay in PFS was felt likely to result in delay in time to treatment-related symptoms and provide a “psychological benefit” to patients. The magnitude of benefit was also considered important, although the ODAC declined to characterize this further. The Committee also expressed concern that approval for first-line treatment of MBC on the basis of PFS alone would inappropriately lower the approval threshold.

The ODAC was divided on the question of whether the reported treatment effect of Avastin in the E2100 trial (HR 0.48, 5.5-month improvement in median PFS), considering the lack of effect on overall survival and additive toxicity of Avastin to standard chemotherapy, constituted substantial evidence of clinical benefit. Four members voted “yes” and five members voted “no” on that question. The ODAC members voting “yes” considered the reported magnitude of the effect important, and were concerned that subsequent therapy could obscure a survival advantage. Those voting “no” had reservations about whether or how prolonging PFS directly benefits patients and questioned the reliability of the reported magnitude of the effect,

---

<sup>28</sup> See Appendix 10 for December 5, 2007, ODAC meeting materials.

given the amount of missing data. In addition, the committee expressed concern over the toxicity profile of Avastin and discussed whether the product could do more harm than good.

#### **E. CDER's Approval of the MBC Indication**

CDER granted accelerated approval of the MBC indication on February 22, 2008. The basis for approval was the magnitude of the PFS effect shown in the E2100 trial.<sup>29</sup> This was a challenging decision for CDER. However, when the safety risks attributed to Avastin were balanced against PFS of *that magnitude*, CDER regarded the risk-benefit analysis as positive.

CDER granted accelerated approval of Avastin's MBC indication based on data showing "an effect on a clinical endpoint other than survival or irreversible morbidity" subject to confirmation of clinical benefit in the required post-approval studies. CDER advised Genentech that its study obligation would be successfully discharged if the confirmatory trials verified the magnitude of PFS improvement and showed no survival impairment. Genentech proposed and CDER agreed that two ongoing trials — AVADO and RIBBON1 — could serve as the required confirmatory studies.<sup>30</sup>

### **V. BASIS FOR PROPOSAL TO WITHDRAW APPROVAL OF AVASTIN FOR MBC**

#### **A. The Clinical Benefit of Avastin in MBC Has Not Been Verified**

Genentech submitted the results from the AVADO and RIBBON1 trials in 2009. Both trials failed to confirm the magnitude of the treatment effect on PFS observed in the E2100 trial,

---

<sup>29</sup> See BLA 125085/91 Office Director Decisional Memo (Richard Pazdur), Appendix 11.

<sup>30</sup> In a submission dated February 15, 2008, Genentech provided its written commitment to verify the results of the E2100 trial through submission of the results of two ongoing trials (AVADO and RIBBON1). Genentech further proposed that "[s]atisfactory review of the results of the . . . AVADO and RIBBON1 studies will be required for the conversion of this accelerated approval." Genentech restated this in its letter of February 20, 2008. See Appendix 12 for the February 15, 2008, letter, and Appendix 13 for the February 20, 2008, letter.

and neither trial showed an improvement in overall survival or in quality of life. Both trials demonstrate serious adverse events, including death, associated with the use of Avastin.

### ***The AVADO Clinical Trial***

The AVADO trial was a double-blind, placebo-controlled, three-arm trial of docetaxel plus placebo, docetaxel plus Avastin 7.5mg/kg, and docetaxel plus Avastin 15 mg/kg. A total of 736 patients with HER2- negative tumors who had not received prior chemotherapy for MBC were enrolled.

In AVADO, the addition of Avastin at a dose of 15 mg/kg to docetaxel yielded a difference of 0.9 months in estimated median PFS between the two arms [HR 0.62 (95% CI: 0.48, 0.70)  $p < 0.0003$ ]. The addition of Avastin at 7.5 mg/kg to docetaxel yielded a difference of 0.8 months in estimated median PFS between the two arms [HR 0.70 (95% CI: 0.55, 0.90),  $p = 0.005$ ]. Objective responses (i.e., tumor shrinkage) were observed in 44% of patients in the placebo arm, 55% in the Avastin 7.5 mg/kg arm ( $p = 0.0295$ ) and 63% in the Avastin 15 mg/kg arm ( $p = 0.0001$ ).

Despite the observed differences in response rate, there was no statistically significant difference in overall survival for the Avastin arms of the trial compared to the control, and mature survival data showed a HR of 1.103 (95% CI 0.84, 1.45) favoring the placebo arm over the 7.5 mg/kg Avastin arm. The HR for overall survival was 1.003 (95% CI 0.76, 1.32) for the 15 mg/kg Avastin arm compared to the placebo arm. In other words, there was no improvement in overall survival attributable to Avastin in the AVADO trial and very little improvement in PFS.<sup>31</sup>

---

<sup>31</sup> Data on health-related quality of life (HRQL) were collected in the AVADO trial, but there was no demonstrated improvement, and results were compromised by missing data. HRQL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) Questionnaire and the Trial Outcome Index (TOI).  
*Continued . . .*

The addition of Avastin to docetaxel resulted in a higher incidence of serious adverse reactions, higher incidence of NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0<sup>32</sup> grade 3-5 adverse reactions, and the occurrence of adverse reactions attributable to Avastin with a 0.8% Avastin-related death rate. A higher incidence of treatment delays and dose reduction of docetaxel was observed in the Avastin arms. There was no improvement in overall survival in either of the Avastin doses, with the hazard ratio favoring the placebo arm over the 7.5 mg/kg dose.

The most common adverse reactions attributable to Avastin reported in the AVADO trial were bleeding/hemorrhage (55%), with the majority of the cases due to epistaxis (grade 1-2), and hypertension (22%). Other clinically significant adverse reactions attributable to Avastin that were reported in this trial were wound healing complications, fistula, gastrointestinal perforation proteinuria and febrile neutropenia. Adverse reactions associated with docetaxel were also increased in incidence and severity in the Avastin-containing arms (diarrhea, palmar-plantar erythrodysesthesia and peripheral sensory neuropathy).

The number of patient deaths clearly attributed to an adverse event was equal across the three arms. Avastin related death in the 15 mg/kg Avastin arm of the trial was 0.8%: one patient died due to gastrointestinal perforation and one died due to pulmonary hemorrhage, adverse reactions that are attributable to Avastin.

### ***The RIBBON1 Clinical Trial***

---

Approximately 15% of the patients in each treatment arm had no baseline screening data and therefore were not evaluable for assessment of the effect of treatment on HRLQ. By week 15, only 64%, 68%, and 73% of the evaluable patients in the placebo, 7.5 mg/kg and 15 mg/kg Avastin arms, respectively, were assessed for HRQL by the FACT-B or the TOI scales.

<sup>32</sup> See Appendix 14 for CTCAE Version 3.0

RIBBON1 was a double-blind, randomized, parallel group trial conducted in women with metastatic or locally recurrent HER 2- negative adenocarcinoma of the breast, who had not received prior chemotherapy for their advanced or metastatic cancer. A total of 1237 patients were randomized (2:1) to receive anthracycline- or taxane-based chemotherapy (n=622) or capecitabine (n=615) in combination with Avastin or placebo. The taxane/anthracycline cohort and the capecitabine cohort were intended to be analyzed separately for comparisons of PFS between chemotherapy and chemotherapy plus Avastin.

The addition of Avastin to anthracycline/taxane-based chemotherapy in the RIBBON1 trial resulted in an improvement in PFS [HR 0.64 (95% CI 0.52, 0.80),  $p < 0.0001$ ], and an observed 1.2-month difference in median PFS times. In the anthracycline/taxane-based chemotherapy arm, the ORR was higher in the Avastin-containing arm (51% vs. 38%,  $p = 0.005$ ). Despite the response rate findings, there was no statistically significant difference in overall survival, and a mature survival analysis yielded a HR of 1.11 (95% CI 0.86, 1.43), favoring the placebo arm of the taxane/anthracycline cohort.

The addition of Avastin to capecitabine also resulted in an improvement in PFS [HR 0.69 (95% CI 0.56, 0.84),  $p < 0.0001$ ], and an observed difference of 2.9 months in median PFS times. The ORR was also higher in the Avastin-containing arm (35% vs. 24%,  $p = 0.01$ ) with the addition of Avastin to capecitabine. There was no statistically significant difference in overall survival. A comparison of the mature survival data for the capecitabine cohort showed a HR of 0.88 (95% CI 0.69, 1.13) favoring the Avastin-containing arm.

Overall, the incidence of NCI CTC version 3.0 grade 3-5 adverse reactions and of serious adverse reactions was almost twice as high in the Avastin arms compared to placebo arms in both cohorts. Adverse reactions known to be caused by Avastin were higher in the Avastin-

containing arms in both cohorts. The most common adverse reactions resulting from Avastin were hypertension, bleeding/hemorrhage and febrile neutropenia. The incidence of grade 3-5 adverse reactions is similar to that currently described in the Avastin package insert. Avastin-related deaths occurred in 1.2% of the patients in the taxane/anthracycline cohort and in the capecitabine cohort.

### ***CDER's Analysis of the AVADO & RIBBON1 Results***

AVADO and RIBBON1 were well-conducted, double-blinded trials. The addition of Avastin to docetaxel (AVADO) and to taxane/anthracycline-based chemotherapy or to capecitabine (RIBBON1) met the pre-specific primary study endpoints, demonstrating statistically significant effects on PFS. However, the magnitude of the improvement in PFS in both trials was substantially smaller than the magnitude of PFS improvement observed in the E2100 trial. In the capecitabine cohort of the RIBBON1 trial, which showed the largest between-arm difference in median PFS times outside of E2100, the 2.9-month improvement in median PFS was roughly half of that reported in the E2100 trial. AVADO and RIBBON1 also failed to show an improvement in overall survival.<sup>33</sup>

Because Avastin's use can result in considerable toxicity, the magnitude of its effect on PFS, especially if not supported by an improvement in overall survival, should be substantial, clinically meaningful, and capable of being confirmed in additional trials. While Avastin's treatment effect on PFS in AVADO and RIBBON1 was statistically significant, its magnitude does not support that Avastin provides a clinically meaningful benefit given the drug's toxicity. The key efficacy variables from all studies submitted by Genentech evaluating Avastin for the treatment of MBC are summarized in tables presented in Appendix 17.

---

<sup>33</sup> See Appendix 15 for CDER's review of AVADO. See Appendix 16 for CDER's review of RIBBON1.

#### 4. *ODAC's Advice*

The ODAC met on July 20, 2010, to review the results of the AVADO and RIBBON1 trials.<sup>34</sup> It voted unanimously (13-0) that the addition of Avastin to docetaxel (AVADO) for the first-line treatment of MBC did not have a favorable risk-benefit analysis, and voted 12-1 that the addition of Avastin to taxanes, anthracyclines or capecitabine (RIBBON1) for the first-line treatment of MBC did not have a favorable risk-benefit analysis. Taking into consideration the totality of findings, and its responses regarding the risk-benefit analyses of the AVADO and RIBBON1 trials, the committee unanimously voted that the AVADO and RIBBON1 results did not provide confirmatory evidence of clinical benefit of Avastin in combination with paclitaxel for the initial treatment of MBC.

The ODAC also reevaluated the risk-benefit analysis for Avastin in MBC based on the more comprehensive data set provided by the AVF 2119g, E2100, AVADO, and RIBBON1 trials. The Committee voted 12 to 1 that the MBC indication should be removed from the Avastin label.

#### **B. Avastin Poses Significant Safety Risks**

The use of Avastin comes with significant safety risks. The addition of Avastin to standard chemotherapy results in an increase in the incidence of adverse reactions of any severity, including serious and grade 3-5 adverse reactions compared with chemotherapy alone. Adverse reactions resulting from Avastin treatment include hypertension, bleeding/hemorrhage, wound healing complications including wound dehiscence, perforation, and fistula/abscess formation. Other adverse reactions resulting from Avastin use include arterial thromboembolic events (stroke, myocardial infarction), venous embolic events, febrile neutropenia, left

---

<sup>34</sup> July 20, 2010, ODAC meeting materials, see Appendix 18.

ventricular dysfunction, and reversible posterior leukoencephalopathy. Avastin-related deaths were observed in 0.8 to 1.7% of patients in breast cancer trials. In the E2100 trial, there was a greater than 20% increase in grade 3-5 toxicities (i.e., severe adverse event, life-threatening adverse event, drug-related death) in the Avastin arm compared to the control arm.

An analysis of selected grade  $\geq 3$  adverse reactions pooled from clinical trials conducted in patients with previously untreated MBC who received taxane therapy, an anthracycline regimen, or capecitabine, with or without Avastin (E2100, AVADO and RIBBON1) shows that although the incidence of specific types of adverse reactions is generally low, the increase in relative risk due to Avastin (compared with chemotherapy alone) is dramatic. There is a more than five-fold increase in the incidence of arterial thrombotic events, severe or life-threatening hypertension, symptomatic left ventricular ejection fraction dysfunction, and severe or life-threatening hemorrhage and a two-fold increase in the incidence of GI perforation, fistula, and febrile neutropenia. Also notable is the development of significant nephrotoxicity manifesting as proteinuria, which is unique to the Avastin treatment arm.

The tables below summarize data characterizing the serious, life-threatening, or fatal adverse reactions (Table 3) resulting from the addition of Avastin to chemotherapy and the overall adverse reactions (Table 5) observed in the AVADO trial, the sole trial in first-line MBC to collect all adverse event data. Only selected adverse reaction data are included in the tables, based on the likelihood that these are attributable to Avastin. Such likelihood is based on safety information (randomized clinical study results and case narrative reports from pre- and post-marketing setting) and on demonstration that such events are more frequent in patients receiving Avastin, or in the case of the AVADO trial, based on higher incidence in the Avastin-containing arm(s) as compared to the placebo-arm.

**Table 3: Pooled Analysis of Selected Grade  $\geq 3$  Adverse Reactions in Patients Treated in the First-Line Setting: Safety-Evaluable Patients (per Genentech)**

Selected Adverse Reactions	Pooled Chemotherapy (n=982)	Pooled Avastin + Chemotherapy (n=1679)
<b>Any adverse event</b>	23%	37%
Neutropenia	7.1%	10%
Sensory neuropathy	8.5%	9.5%
Hypertension	1.2%	9%
Febrile neutropenia	3.5%	6.5%
Venous thromboembolic event	3.8%	2.8%
Proteinuria	0	2.3%
Arterial thromboembolic event	0.3%	1.6%
Left ventricular systolic dysfunction	0.2%	1.5%
Hemorrhage	0.4%	1.5%
Abnormal Tissue Repair	0.8%	1.7%
Wound dehiscence	0.3%	0.8%
Fistula	0.3%	0.5%
GI perforation	0.3%	0.5%
RPLS	0	<0.1%

\* Source: Genentech Inc., *Integrated Summary of Safety Appendix B, Table 53, page 202*

These risks are described in Avastin’s labeling, and they are not new. However, the available data may underestimate the risks associated with Avastin because only two of the four studies collected information on **all** adverse events. For example, only grade 3-5 toxicity data were collected in the E2100 trial, and no information was collected on adverse reactions that resulted in discontinuation of therapy because of toxicity. Similarly, no information was collected in E2100 that would permit a characterization of the duration of toxicity or of complete resolution of toxicity.

The limitations noted above and similar limitations in the RIBBON1 trial, described in the table below, present difficulties in characterizing the risks of Avastin for patients with MBC.

**Table 4: Comparison of Adverse Event Collection in E2100, AVADO, and RIBBON1**

Type of Adverse Event	E2100	AVADO	RIBBON1
Non-serious Adverse Event by NCI CTCAE grade			
Grade 1-2	None	All	Selected Avastin toxicities
Grades 3	Non-hematologic only	All	Selected Avastin toxicities
Grades 4-5	Hematologic and non-hematologic	All	Selected Avastin toxicities
Serious Adverse Events	Avastin arm only	All	All
Adverse Events leading to dose modification/discontinuation			
Chemotherapy	None	All	None
Avastin	None	All	Only if Avastin discontinued

The following table displays the per-patient incidence of Avastin adverse reactions of any severity and of grade 3 or higher severity, by treatment arm in the AVADO trial, the only trial in first-line treatment of MBC with collection of **all** adverse events occurring during protocol treatment.

**Table 5: Selected\* Adverse Event in the AVADO Trial by Treatment Arm**

AE (MedDRA PT)	Placebo + Doc N=231		Avastin 7.5 + Doc N=252		Avastin 15.0 + Doc N=247	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
At least one AE	85.7%	35.5%	91.3%	42.5%	91.1%	43.7%
Bleeding	29%	0.9%	54%	1.2%	55%	1.2%
Epistaxis	20%	0.4%	48%	0.4%	49%	0.4%
Hemorrhage (other)	10%	0.4%	6%	0.8%	6%	0.8%
Neutropenia	22%	20%	23%	21%	23%	21%
Febrile neutropenia	12%	12%	16%	15%	18%	17%
Hypertension	10%	1.3%	14%	0.8%	22%	4.5%
Sensory neuropathy	62%	2.2%	64%	3.2%	58%	4.5%
Venous thromboembolic events	8%	3.5%	6%	1.6%	7%	1.2%
Wound dehiscence	1.3%	0.9%	3.2%	0.4%	4.9%	0.4%
Proteinuria	1.7%	0	2.0%	0.8%	8%	2.0%
Fistula and abscess	0.4%	0.4%	2.4%	0.8%	2.8%	0.8%
LV systolic dysfunction	0.4%	0	1.6%	1.2%	0.8%	0
Gastrointestinal perforation	0.9%	0.9%	0.4%	0.4%	0.4%	0.4%
Arterial thromboembolic events	0.9%	0.4%	0	0	1.6%	0.1%

\* Limited to adverse reactions of Avastin identified in previous controlled studies.

### **C. The Risk-Benefit Balance in MBC Is Unfavorable**

Avastin appeared to have a clinically important treatment effect on PFS (subject to verification), as evidenced by the magnitude of the effect in a single, randomized trial. However, four other clinical trials of Avastin in MBC (AVF2119g, AVADO, RIBBON1, and RIBBON2<sup>35</sup>), all of which were submitted by Genentech to the Avastin BLA, showed either no effect or a much smaller effect on PFS than in the E2100 trial, ranging from no improvement to 2.9 months.

Moreover, all five breast cancer trials (E2100, AVADO, RIBBON1, RIBBON2, and AVF2119g) using Avastin have failed to demonstrate a statistically significant prolongation of overall survival (please refer to Appendix 20 for survival curves). The improvement in ORR (10-19%) was modest.

Particularly when viewed in light of the totality of the clinical trial data, the E2100 trial results are questionable for several reasons. First, it is unlikely that a 5.5-month improvement in median PFS could be present without an improvement in overall survival. Furthermore, E2100 is less methodologically rigorous than the other four trials. For example:

---

<sup>35</sup> The RIBBON2 trial (also referred to as the AVF3693g trial) is a double-blind, placebo controlled, international trial conducted by Genentech to evaluate the safety and efficacy of Avastin in combination with taxanes, capecitabine, or gemcitabine in patients who have received prior chemotherapy for metastatic HER2-negative breast cancer. The results of RIBBON2 in conjunction with the results of AVF2119g were submitted by Genentech on July 16, 2010 to support an efficacy supplement seeking approval of Avastin in combination with taxanes, capecitabine or gemcitabine for use in patients who have received prior chemotherapy for metastatic HER2-negative breast cancer, as well as to support removal of a limitations of use statement from the current INDICATIONS AND USAGE section (1.3) of the Avastin label regarding Avastin's not being indicated for patients with breast cancer that had progressed following anthracycline and taxane chemotherapy administered for metastatic disease. CDER relied on its evaluation of the E2100, AVF2119g, AVADO, and RIBBON1 trials to determine that post-approval clinical trials failed to verify clinical benefit (21 CFR 601.43(a)(1)). CDER appropriately took the results of the RIBBON2 trial into account in determining that "other scientific evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use" (21 CFR 601.43(a)(6)). See Appendix 19 for CDER's review of RIBBON2.

- The E2100 results are based on an interim analysis. Trials terminated based on interim results carry higher risks that larger-than-expected treatment effects are chance findings (i.e., analysis of data at a “random high”).<sup>36</sup>
- The E2100 trial design did not adequately control for bias in measuring the subjective PFS endpoint. When the primary study endpoint is based on tumor measurements, tumor endpoint assessments generally should be verified by central reviewers blinded to study treatments; this is particularly important for open-label (not blinded) studies such as E2100.
- Independent verification of the PFS endpoint in E2100 was made uncertain by missing data. A substantial number of patients were not followed until disease progression as determined by the independent reviewers due to inability to locate scans (10%) or were lost-to-follow-up prior to the data cut-off date for the final analysis (34%).
- The E2100 trial was open-label (not blinded) whereas the AVADO, RIBBON1, and RIBBON2 trials were blinded and placebo-controlled. (The AVF2119g trial was also open-label, but had a pre-specified plan for collection of radiographic data and for analysis of tumor-based endpoints by an independent review committee, masked to treatment assignment, leading to fewer missing scans.)

The treatment effects seen in the breast cancer trials are modest at best and must be weighed against the risks associated with Avastin.

The totality of the data on Avastin for MBC support that the clinical benefit based on PFS seen in the E2100 trial was an outlier. The magnitude of that clinical effect has not been

---

<sup>36</sup> See generally: Montori VM, Devereaux PJ, Adhikari NKJ, et al., Randomized Trials Stopped Early for Benefit: A Systematic Review. *JAMA* 294: 2203-2209, 2005; Heffner AC, Milbrandt EB, Venkatamaran R, Trials stopped early for benefit? Not so fast! *Critical Care* 11:305, 2007; Pocock SJ and Hughes MD, Practical Problems in Interim Analyses, with Particular Regard to Estimation. *Controlled Clinical Trials* 10: 209S-221S, 1989; Ioannidis JP, Contradicted and Initially Stronger Effects in Highly Cited Clinical Research *JAMA* 294: 218-228, 2005.

confirmed in subsequent trials, and thus there is no evidence that Avastin for MBC provides a clinical benefit to patients. For these reasons, the risks of Avastin outweigh its benefits for the treatment of MBC.

## **VI. CDER's RESPONSE TO GENENTECH'S ARGUMENTS AGAINST WITHDRAWAL**

Genentech cannot dispute that the post-marketing studies of Avastin failed to demonstrate the magnitude of PFS seen in the E2100 trial or that Avastin has not been shown to improve overall survival or quality of life for MBC patients. Instead, Genentech argues that FDA should “maintain” approval for the MBC indication while the company designs and conducts new clinical trials in an effort to establish the efficacy of the drug in combination with various chemotherapy agents. Genentech also argues that the Agency should consider several publications that, it argues, contain new information consistent with the results of E2100. In addition, Genentech downplays the safety risks associated with Avastin and asserts that certain of the side effects – hypertension and proteinuria – can be “managed.” Finally, Genentech contends that CDER is seeking to apply new approval standards to drugs that treat first-line MBC and that the Center’s decision is contrary to the decisions of other authorities.

Genentech’s arguments against withdrawal are incorrect, unpersuasive, and irrelevant.

### **A. Genentech’s Position that FDA Should "Maintain Approval" for Avastin in MBC Is Inconsistent With the Regulatory Framework and the Interests of the Public Health**

Genentech contends that the Agency should “maintain” accelerated approval of Avastin’s MBC indication while the company plans and conducts additional clinical trials, perhaps identifying a subset of MBC patients who are likely to benefit from treatment. (See Genentech’s

January 16, 2011, Submission to the Docket (“Genentech Response to NOOH”) at 16.) CDER strongly disagrees with this approach, for numerous reasons.

First, CDER has determined, after an extensive review of voluminous data, that the risks of Avastin outweigh the benefits in treating MBC and, therefore, that it is in the interest of public health that the MBC indication be withdrawn.

Second, the accelerated approval regulations and the FD&C Act contemplate that the Agency will withdraw approval if the post-approval clinical trials fail to verify clinical benefit or if other evidence demonstrates that the product is not safe or effective under its conditions of use. CDER has authority to withdraw approval of Avastin under these circumstances, and CDER has determined, exercising its scientific judgment, that it should do so here.

Third, CDER’s ability to withdraw approval expeditiously when confirmatory trials fail to verify clinical benefit or other evidence demonstrates a product is not safe or effective is central to the accelerated approval program.

Finally, because Avastin is approved for several other cancer indications, it will remain available as a treatment option for those physicians and patients who believe, despite withdrawal of the MBC indication, that an individual patient may benefit from the use of the drug.

Genentech asserts that “[s]o 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.” (Genentech Response to NOOH at 16 (emphasis added).) This language confuses the standard applicable to accelerated approval decisions in § 601.41 of the regulations (referring to surrogate endpoints *reasonably likely to predict clinical benefit*) with the standards applicable to

withdrawal actions in § 601.43 of the regulations and section 506(b) of the FD&C Act. The *reasonably likely* language refers only to the relationship between a surrogate endpoint and clinical benefit. In the case of Avastin’s MBC approval, there was no surrogate endpoint – CDER believed that 5.5 months of PFS could be deemed a clinical benefit, subject to confirmatory trials. More than a *reasonable likelihood* of clinical benefit was expected when Avastin’s MBC indication was granted accelerated approval; the Center expected the post-approval studies to *confirm* that benefit, not merely to maintain a “likelihood” that the drug provided a clinical benefit.

Implicit in Genentech’s suggestion that it may identify a subset of patients for whom Avastin is more effective in treating MBC is an acknowledgment that Avastin may have a favorable risk-benefit profile in only a subset of HER2-negative MBC patients. Patients and physicians must be able to rely on FDA-approved indications. Because the approved MBC indication is not supported by substantial evidence that Avastin is safe and effective for that indication, as required under the Agency’s drug approval standards, approval should be withdrawn.

Genentech does not explain how it would enroll patients in a new, blinded, controlled clinical trial studying the use of Avastin in combination with paclitaxel to treat MBC if this were to remain an approved indication. Patients generally do not enroll in trials in which an approved indication is tested against a placebo (in this case, paclitaxel plus a placebo). Furthermore, even if Genentech were able to complete new trials showing Avastin has a favorable risk-benefit balance when used to treat a subset of HER2-negative MBC patients, this work would likely take many years. The accelerated approval regulations contemplate and provide for expedited withdrawal of approval when the required confirmatory trials fail to verify clinical benefit, as

with the AVADO and RIBBON1 trials. Rather than serving as a basis to “maintain” approval, which is not part of the accelerated approval program, the new research proposed by Genentech, if completed favorably, could be used to support a new sBLA requesting an MBC indication.

**B. Genentech’s Hypothesis Regarding Different Chemotherapy Partners Is Not Supported by the Data**

Based on the data from the AVADO and RIBBON1 trials, Genentech hypothesizes that the specific chemotherapy partner with which Avastin is used will influence the magnitude of the drug’s effect in treating MBC. The company argues that the MBC approval for Avastin should be maintained while it conducts further studies with paclitaxel, the chemotherapy partner used in the E2100 trial.<sup>37</sup> As discussed above, maintaining approval for an indication for which clinical benefit has not been confirmed, while the company designs and conducts additional trials, is inconsistent with the accelerated approval framework and the interests of the public health.

Genentech argues that because the chemotherapy partner influences the magnitude of the treatment effect, only data generated with that chemotherapy partner are relevant to verifying the benefit of Avastin in combination with paclitaxel. Genentech claims that the lower magnitude of effect on median PFS in the AVADO and RIBBON1 trials is an observation consistent with clinical experience that some chemotherapy agents (and their dose and schedule) yield different levels of treatment effect.<sup>38</sup> Genentech thus contends that the lesser improvement in PFS in these confirmatory trials merely suggests that the choice of different chemotherapy partners in each of

---

<sup>37</sup> Genentech Response to NOOH (Appendix 9) at 28.

<sup>38</sup> Genentech Response to NOOH (Appendix 9) at 17.

the trials may influence the magnitude of benefit observed in each trial, and not that the AVADO and RIBBON1 trials invalidate the findings of the E2100 trial.<sup>39</sup>

To support its assertions, Genentech postulates that 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.”<sup>40</sup> This hypothesis, as Genentech itself concedes, remains unproven.

***Genentech’s Hypothesis Has Not Been Substantiated by Either Clinical or Non-Clinical Evidence.*** As CDER has explained, “[a]ssertions that there is a unique interaction between Avastin and paclitaxel providing a rationale for the magnitude of PFS change observed only in E2100 has not been substantiated by either clinical or non-clinical evidence.”<sup>41</sup>

Genentech does not disagree. Genentech argues, however, that because the magnitude of the treatment effects observed with different chemotherapy partners is different, those differences must be due to the use of different chemotherapy partners.

To support this argument, CDER expects that there should be some proven scientific basis for substantial differences, such as evidence of drug interactions or synergistic/overlapping toxicity between Avastin and other chemotherapy drugs. There is none. To the contrary, all evidence submitted to date (e.g., population pharmacokinetic analyses) indicates that there are no unique interactions between Avastin and any of the chemotherapy partners administered in the trials. In the absence of a scientifically supported basis for chemotherapy-specific interactions,

---

<sup>39</sup> Genentech Response to NOOH (Appendix 9) at 2-3, 18, 25-29.

<sup>40</sup> Genentech Response to NOOH (Appendix 9) at 28.

<sup>41</sup> Office Director Memo, December 15, 2010 (Appendix 21) at 5.

the more likely explanation for the failure of the clinical trials to verify the results of the E2100 trial is that the magnitude of the PFS treatment effect observed in E2100 is an outlier.

***The E2100 Trial Was Not Designed to Illustrate that Duration of Chemotherapy Influences Magnitude of PFS.*** Genentech acknowledges that “the scientific basis for the observed differential effect of Avastin with paclitaxel is not yet understood.”<sup>42</sup> Genentech asserts, however, that “[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.”<sup>43</sup> Specifically, Genentech proposes that chemotherapies providing for prolonged combined exposure with Avastin yield the strongest treatment effects. E2100 specified that paclitaxel be administered for a maximum of eighteen 4-week cycles; a March 9, 2004, amendment to the protocol allowed treatment to continue until disease progression. In contrast, the protocols for AVADO and RIBBON1 specified a maximum of nine 3-week cycles of docetaxel and eight 3-week cycles of anthracyclines.

The designs of the E2100, RIBBON1, and AVADO trials vary with regard to maximum permissible duration of chemotherapy. However, the E2100 trial was not adequate in design to test the hypothesis as to whether treatment outcomes will differ based on the duration of paclitaxel therapy. This was not a variable included in the study design. The duration of treatment is an outcome of the efficacy variable tested, i.e., duration of treatment is dependent both on an absence of toxicity and a determination of non-progressing disease. The longer duration of treatment in the experimental arm of E2100 may be due, at least in part, to the

---

<sup>42</sup> Genentech Response to NOOH (Appendix 9) at 2.

<sup>43</sup> Genentech Response to NOOH (Appendix 9) at 3.

determination by investigators in the open-label E2100 trial that patients receiving the investigational treatment had not exhibited disease progression. In order to test this hypothesis, a randomized trial specifically testing the question of whether the number of chemotherapy cycles administered (e.g., nine or fewer vs. treatment until disease progression) in combination with Avastin resulted in better progression-free or overall survival would be needed, similar to the trial designs for studies included in the recent meta-analysis evaluating the effects of duration of chemotherapy on clinical outcomes.<sup>44</sup> In the absence of an appropriate study directly testing and confirming this hypothesis, it is not possible to determine what effect, if any, duration of concurrent chemotherapy administration has on treatment outcomes.

***Genentech’s Argument that Differences in Magnitude of Treatment Effect are the Result of Different Chemotherapy Partners is Contrary to Genentech’s Prior Position and is Unpersuasive.*** Genentech’s position that differences in treatment effect are the result of different chemotherapy partners is new.<sup>45</sup> Genentech first sought broad approval of Avastin in combination with all taxane-based chemotherapy partners based solely on the results of the paclitaxel-specific E2100 trial.<sup>46</sup> At that time, Genentech argued that the paclitaxel study could

---

<sup>44</sup> Genmari A, Stockler M, Puntoni M, et al. “Duration of Chemotherapy for Metastatic Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Clinical Trials” J Clin Oncol: 4 April 2011 (e-pub ahead of print).

<sup>45</sup> The hypothesis that Avastin is significantly more effective against MBC when combined with paclitaxel than with other chemotherapy drugs was not identified to CDER until after the NOOH seeking to withdraw the indication was issued.

<sup>46</sup> To confirm an indication for combination use with paclitaxel, Genentech proposed, and CDER agreed, that Genentech could rely on studies of Avastin in combination with chemotherapy drugs other than paclitaxel. As correctly identified in the Notice of Hearing, these studies were chosen because they were already ongoing at the time of the initial approval and both CDER and Genentech believed, at that time, that the results of these studies could provide evidence to verify the claim that Avastin, combined with paclitaxel, would have the effect indicated in the approved labeling (76 Fed. Reg. 27335). This practice stems largely from practical considerations. It would be very difficult to enroll patients in a blinded clinical trial involving an approved indication because they would prefer to obtain treatment outside of the trial and not risk being assigned to the placebo or control arm. Generally, CDER believes that this approach can further characterize the risks and benefits of the drug — thus fulfilling the post-approval requirement to confirm clinical benefit under accelerated approval — while still allowing the applicant the

*Continued . . .*

support a broad taxane-based chemotherapy indication because “all taxanes, at either of the two common schedules, are frequently used in the treatment of MBC because the literature supports considering taxanes as a class of cytotoxic agent based on their similar efficacy and safety in the treatment of MBC.”<sup>47</sup>

Genentech also argues that CDER’s recommendations in the January 10, 2006, meeting on the RIBBON1 trial support Genentech’s position that treatment outcomes differ based on the chemotherapy partner. CDER requested that Genentech design RIBBON1 to independently evaluate and confirm the presence of an Avastin treatment effect in the capecitabine cohort. This request arose from CDER’s concerns regarding the absence of a clear explanation for the discrepancy in the findings of the E2100 and the AVF2119g trials, *i.e.*, a finding of a substantial effect on PFS in one trial and the finding of no effect on PFS in the other trial. Among the possible hypotheses for this finding, one that had not been adequately investigated was the possibility of unrecognized drug interactions. This specific request was driven by the results of the clinical program for Avastin in MBC and derives from consideration of the totality of the data rather than a general policy to consider each drug combination a distinct experiment that cannot be generalized.

At bottom, Genentech’s argument that Avastin may be more effective with different chemotherapy parties is not supported by the available data. The MBC indication for Avastin should not remain approved while Genentech designs and conducts studies in an effort to prove its hypothesis.

---

opportunity to obtain approval of an expanded indication for the drug (and, therefore, added incentive to complete the trial(s)).

<sup>47</sup> STN BL 125085/91 section 2.5.1 at 8.

**C. Genentech’s Claim That CDER Has Changed its Approval Standards Is Incorrect**

Genentech argues that CDER’s proposal to withdraw approval of Avastin’s MBC indication reflects a new standard for the demonstration of efficacy required to support a first-line MBC indication. More specifically, Genentech asserts that CDER now considers PFS improvement inadequate unless it is “of a large (but unspecified) magnitude” and that otherwise approval must be supported by an improvement in overall survival (Genentech Response to NOOH at 43). Genentech asserts throughout this argument that such new policies were developed without public input, are inappropriately demanding, and will hamper the development of cancer drugs. None of these assertions has merit.

CDER’s standards in this area have not changed, and nor are they inappropriately demanding. Cancer treatments must show clinical benefit to patients, meaning a favorable risk-benefit balance. This standard is clearly embodied in the FD&C Act and in FDA’s regulations.

As discussed above in section III.B (Confirmation of Clinical Benefit), CDER’s views regarding PFS as a clinical endpoint in oncology trials are expressed in published guidance. The guidance makes it clear that PFS, along with a variety of other clinical endpoints, can be used to support drug approval. CDER also has consistently applied the view of PFS articulated in that guidance to approval decisions, and the approval of Avastin for MBC in CDER’s accelerated approval decision underscores that.

Genentech correctly represents that an effect on PFS alone may not be adequate to support FDA approval unless the effect is of a sufficient magnitude. This standard is not new. CDER’s view that “whether an improvement in PFS represents a direct clinical benefit . . .

depends on the magnitude of the effect and the risk-benefit of the [drug] compared to available therapies” has been stated in published guidance since 2007.<sup>48</sup>

CDER articulated this standard directly to Genentech beginning as early as 2004. During an October 28, 2004, teleconference regarding the design and analysis plan for the E2100 trial, Genentech asked whether PFS would be an adequate endpoint for full approval. CDER informed Genentech that it would depend on the overall dataset and magnitude of PFS.<sup>49</sup> CDER does not and cannot commit to a specific magnitude of effect in advance of a clinical trial’s completion because outcomes will vary based on factors such as the toxicity profile of the drug being investigated. New treatments approved since initiation of a clinical trial may have an impact on whether an investigational treatment qualifies for accelerated approval as providing meaningful therapeutic benefit over existing treatments.

CDER continued to provide consistent advice during discussions with Genentech in 2006 and 2009. During a January 10, 2006, teleconference, Genentech expressed concern about whether survival data were needed for regular approval. CDER stated that “whether the [PFS] data provided will support regular approval “depends on the strength of the data and the effect size. . . .”<sup>50</sup> At a meeting on February 26, 2009, CDER again indicated that it could not say

---

<sup>48</sup> FDA guidance for industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007) at 8 (Appendix 5). FDA announced the availability of a draft of this guidance in the *Federal Register* on April 4, 2005 (70 Fed. Reg. 17095). The Agency took into consideration comments received from industry, professional societies, and consumer groups in finalizing this guidance. Availability of the final guidance was announced in the *Federal Register* of May 16, 2007 (72 Fed. Reg. 27575). As with all finalized FDA guidance documents, the public may comment on this guidance at any time (21 CFR 10.115(g)(5)), and FDA will review comments received and revise the document as appropriate.

<sup>49</sup> Minutes of October 28, 2004, Teleconference, see Appendix 22.

<sup>50</sup> Memorandum of Teleconference, January 10, 2006, at 3, see Appendix 23.

whether “PFS data alone [would] support full [i.e., regular] approval/conversion of Avastin for first-line treatment of patients with MBC.”<sup>51</sup>

In summary, CDER’s proposal to withdraw Avastin’s MBC indication is based on (1) the failure of the AVADO and RIBBON1 trials to verify clinical benefit and (2) the totality of available data pointing to a lack of safety and effectiveness. When making both determinations, CDER appropriately considered risks and benefits. CDER has not changed its views regarding the usefulness of PFS as a clinical endpoint for the approval of cancer drugs and has not determined that an overall survival benefit is always needed in addition to a PFS improvement. In other words, CDER has not in any way sought to “move the goal posts.” CDER has not determined that a set magnitude of PFS improvement is needed to support an MBC indication; however, CDER has determined that the magnitude of PFS improvement shown in Avastin’s MBC post-approval studies, and shown in the totality of the relevant data, is so small that the risk-benefit balance is unfavorable.

**D. Genentech’s Efforts to Downplay the Serious Safety Risks Associated With Avastin Are Misleading**

Genentech tries to minimize certain risks associated with Avastin by arguing that “the more common adverse events associated with Avastin are clinically manageable such that treatment can be continued.” The company states:

[M]ost 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.<sup>52</sup>

---

<sup>51</sup> Memorandum of Meeting Minutes, Feb. 26, 2009, at 3-4, see Appendix 24.

<sup>52</sup> Genentech Response to NOOH (Appendix 9) at 32.

Genentech has not fully characterized the long-term consequences of either hypertension or proteinuria in patients with MBC, nor has it characterized the long-term outcomes of hypertension in any population. The potential for persistent hypertension is recognized in the *Warnings and Precautions* section of the Avastin product label, which recommends that practitioners “continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuation of Avastin.” Due to the lack of data regarding the short- and long-term consequences of Avastin-induced or Avastin-exacerbated hypertension, Genentech committed — when Avastin was first approved in 2004 — to provide data “characterizing the incidence and clinical course (including duration and medical management) of hypertension in patients during treatment and following the discontinuation of Bevacizumab and in concurrent control patients. This will be evaluated in 2700 subjects, enrolled in the planned NSABP trial, C-08, of whom 50 percent will be randomized to receive Bevacizumab.”<sup>53</sup>

The available data regarding the long-term effects of proteinuria are also limited. In a single trial conducted in patients with renal cell cancer, the overall incidence of proteinuria (all grades) was 20%. In this trial, the median time to development of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. While the median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months), proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent

---

<sup>53</sup> Avastin Approval Letter (Feb. 26, 2004), see Appendix 6.

discontinuation of Avastin in 30% of the patients who developed proteinuria in this trial.

Genentech has also committed to further study of Avastin-induced proteinuria.<sup>54</sup>

These common side effects of Avastin are not benign. Hypertension does not resolve in all patients at the end of treatment with Avastin, sometimes causing an MBC patient to need long-term pharmacologic therapy. Similarly, nearly 40% of patients with grade 3 proteinuria did not have evidence of resolution, and for those who did, resolution took months. Because at least half of patients receiving initial treatment for MBC can expect to live for several years, these risks are not acceptable in light of Avastin's minimal or lack of effect on PFS.

#### **E. Genentech's Reliance on Decisions of Other Authorities Is Misplaced**

Genentech argues that some "independent scientific decision-makers have reaffirmed the value of Avastin in combination with paclitaxel" for MBC. This statement is out of context and irrelevant to the issue before the Presiding Officer, and does not alter CDER's analysis of the data. The other decision-makers to which Genentech refers operate under different frameworks, often apply different criteria than FDA applies, and may base their decisions on different data or different scientific judgment.

***European Medicines Authority (EMA).*** Genentech notes that the EMA recently concluded that "the benefits of Avastin in combination with paclitaxel outweigh its risks" for the initial treatment of patients with MBC. CDER agrees that its regulatory decisions on Avastin differ from those of the EMA and reflect different scientific conclusions by the two regulators. This is true not only with regard to the MBC indication for Avastin, but also with regard to the

---

<sup>54</sup> Avastin Approval Letter (Feb. 26, 2004) (describing the following commitment: To assess for risk factors associated with proteinuria by prospectively collecting and analyzing data to characterize the incidence and clinical course (including duration) of proteinuria in patients during treatment with Bevacizumab and following the discontinuation of Bevacizumab and in concurrent control patients. This will be evaluated in 2700 subjects, enrolled in the planned NSABP study, C-08, of whom 50 percent will be randomized to receive Bevacizumab).

use of Avastin for treatment of glioblastoma multiforme, where CDER granted approval for the indication, but the EMA did not. With regard to the scientific difference for Avastin in MBC, that difference is largely limited to the risk-benefit analysis for Avastin in combination with paclitaxel. CDER and the EMA are otherwise largely in agreement about the meaning of the data. Moreover, some of the differences in the regulatory decisions of CDER and the EMA are attributable to differences in the respective regulatory frameworks.

The basis for the EMA approval of the MBC indication was, as it was for CDER, the E2100 trial. Like CDER, the EMA viewed the 5.5 month increase in the median duration of PFS in E2100 as “clinically and statistically significant[.]” The essence of the disagreement is that EMA views the data from E2100 as sufficient, considering only data obtained with use of Avastin in combination with paclitaxel, to show that Avastin has a favorable risk-benefit balance in MBC, while CDER believes that the results of E2100 must be considered in the context of the other trials using different chemotherapy partners, as discussed above. Indeed, the contradictory findings of the E2100 and AVF2119g trials influenced CDER’s decision to approve Avastin’s MBC indication under the accelerated approval framework and require Genentech to conduct and submit confirmatory post-approval studies.

In addition to this difference, in deciding to extend the indication for Avastin, the EMA also relied on earlier findings with fewer analyses. The EMA relied on the investigator-assessed analysis of PFS as the primary efficacy analysis, as the independent review was still ongoing when the EMA made its decision. The EMA chose not to wait for the independent review, because “sensitivity analyses, conducted by the MAH [marketing authorization holder] with the aim of assessing the impact of a potential investigator bias, provide reassurance that the substantial prolongation in PFS in the bevacizumab arm is unlikely to be attributable to bias.” In

addition, the EMA relied on an interim analysis of overall survival (with 377 of the planned 481 events), which indicated the effects on survival might be favorable.

The EMA granted regular approval of Avastin in combination with paclitaxel for the first-line treatment of MBC on February 22, 2007: exactly one year before CDER approved Avastin’s MBC indication. Because Avastin received a regular approval for its first European Union (EU) marketing authorization — for colorectal carcinoma in January 2005 — no supplemental indication (including the MBC indication) was eligible for conditional approval in the EU.<sup>55</sup> Conditional approval in the EU is analogous to accelerated approval in the United States in that post-approval studies are required.

Similarly, in the EMA’s assessment of the AVADO trial, the EMA considered both the final analysis of PFS and an unplanned, exploratory analysis of PFS using a later cut-off date (which demonstrated a larger difference in median PFS than the final PFS analysis) to conclude the risk-benefit ratio for the addition of Avastin to docetaxel in the first-line treatment of MBC was favorable. Specifically, EMA considered PFS results from the AVADO trial that were updated following the data cut-off date of October 31, 2007. The public assessment report states that “[w]ith the updated analyses presented, the difference was modest, with a median prolongation of PFS of 2 months for the patients in the high dose bevacizumab arm compared to the control arm. With the updated analyses, the improvement in PFS was seen at a follow-up for up to 18 months. This increased improvement in PFS with the updated analyses can be regarded as clinically relevant.” CDER limited its review to the PFS data collected on or before the pre-specified cut-off date of October 31, 2007, because the analyses based on the later cut-off date

---

<sup>55</sup> EMEA Guideline on the Scientific Application and the Practical Arrangements Necessary to Implement Commission Regulation (EC) No 507/2006 on the Conditional Marketing Authorisation for Medicinal Products for Human Use Falling Within the Scope of Regulation (EC) No 726/2004 (December 2006). See Appendix 25 for a copy of this guideline.

were considered exploratory. The EMA also considered the differences in the overall response rates (64% in the high-dose Avastin arm compared to 46% in the placebo arm) and the modest difference in time to treatment failure (7.9 months versus 6.3 months) as supportive efficacy data. In contrast, CDER considered these differences to be modest and not supportive of a favorable risk-benefit assessment.

Upon receipt of the results of the RIBBON1 trial, the European Commission requested, under Article 20 of Regulation (EC) No. 726/2004 (on September 23, 2010), that the Committee for Medicinal Products for Human Use (CHMP) assess all data available on Avastin in combination with paclitaxel or docetaxel in first-line treatment of MBC and opine on whether the marketing authorization in this indication should be maintained, varied, suspended or revoked. Upon conclusion of the CHMP review in April 2011, the CHMP adopted a positive opinion for a limited indication supported by the RIBBON1 trial and did not modify its negative opinion from December 2010, based on re-analysis of the AVADO trial.

- Regarding use with docetaxel, the CHMP recommended that approval of this indication be withdrawn. This recommendation was based on the “very modest benefit observed in the [AVADO] trial” with no effect on overall survival and the results observed in patients receiving Avastin plus docetaxel in the RIBBON2 study, which showed an extremely modest effect on PFS and a “negative trend” in overall survival among patients receiving this combination.
- Regarding use with capecitabine, and based on the Committee’s recommendation, the EMA limited approval of Avastin to MBC patients for whom treatment with other chemotherapy options, including taxanes or anthracyclines, is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant

setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine.

- Regarding use with paclitaxel, the Committee determined that the benefit-risk balance was unchanged, noting that “the observed effect in terms of progression-free survival is not questioned, even in the absence of a clear effect on overall survival.” The Committee also noted that the magnitude of the effect observed in the Avastin plus abraxane subgroup of [RIBBON1] was smaller than that observed in E2100, and determined this finding to be “of limited relevance due to the different types of agents.”

The EMA and CDER are in general agreement that:

No clinical trial has demonstrated that Avastin improves overall survival of patients with MBC.

- No clinical trial has demonstrated that Avastin improves the health-related quality of life of patients with MBC.
- Despite limitations in the safety data collected in E2100 as discussed previously in this document (See Section IV.B, “Avastin Poses Serious Safety Risks”), the E2100 trial showed an increase in serious adverse drug reactions for sensory neuropathy (16.5% vs. 23.2%), hypertension (1.4% vs. 15.5%), fatigue (4.9% vs. 8.6%), and proteinuria (0.0% vs. 3.0%) with the addition of Avastin to paclitaxel over paclitaxel alone.

***NCCN Clinical Practice Guidelines.*** Genentech argues that the ODAC recommendation to withdraw approval of the MBC indication should be discounted because the National Comprehensive Cancer Network (NCCN) Breast Cancer Panel, which Genentech asserts has more specialized breast oncology expertise and clinical experience with Avastin and therefore is better able to evaluate its risk-benefit ratio than the ODAC, affirmed its recommendation for use

of Avastin in combination with paclitaxel in its 2010 Clinical Practice Guidelines for Breast Cancer.

It is not clear what Genentech means by “specialized breast oncology expertise.” Breast cancer is one of the most common cancers in the United States, and therefore is considered part of general oncology expertise. Every medical oncologist is trained to treat it. There is also no board certification or official recognition for a breast cancer specialty. Further, CDER has great confidence in the ODAC, including its expertise in breast cancer. The July 2010 ODAC included four regular voting members who have authored numerous publications regarding breast cancer treatment (Drs. Freedman, Grem, Loehrer, and the Chair, Dr. Wilson). Two temporary voting members, Drs. Buzdar and Mortimer, were appointed to serve on the July 2010 ODAC specifically because of their breast cancer expertise.

The NCCN, a consortium of 21 cancer centers in the United States, has members with considerable clinical experience and expertise in oncology treatment. However, it is not a regulatory entity. As such, its standards for both conflicts of interest and scientific decision-making in the development of its clinical practice guidelines are different than CDER’s. The goal of the NCCN Guidelines is to help oncologists make the major clinical decisions encountered in managing their patients by providing ready access to synthesized information. The NCCN Guidelines™ are composed of recommendations, based on the available evidence at the time they are derived, on treatment options for sequential management decisions and interventions for the malignant cancers that affect 97 percent of all patients with cancer. Separate guidelines relate to major prevention and screening topics and another set of pathways focuses on the major supportive care areas. Unless otherwise specified, all recommendations in the

NCCN Guidelines are Category 2A (i.e., the recommendation is based on lower-level evidence and there is uniform NCCN consensus).

In contrast, the ODAC relies on summary of data provided by the sponsor (or applicant) as well as by CDER derived from the patient-level data. In presentations, both the sponsor or applicant and CDER provide information regarding the completeness, accuracy, and quality of the data, including the results of clinical study site audits, when conducted. The ODAC's recommendations are based on high-level evidence (two or more adequate and well-controlled trials or a single, well-controlled trial with supportive evidence from prior approvals or other clinical data). Furthermore, ODAC members receive specific training in the legal requirements for drug approval to which FDA must adhere.

The level of scrutiny for potential conflicts of interest for ODAC and temporary voting members far exceeds those undertaken by the NCCN. Similar to the NCCN procedures, ODAC members must self-report financial conflicts of interest prior to each meeting. In contrast to the NCCN procedures, Special Government Employees (SGEs) invited to serve on FDA Advisory Committees are screened against a competing/affected product list that is compiled based on the product at issue and its indication. The scope of products included on this list includes all products that may be affected either positively or negatively by the outcome of the Advisory Committee meeting, not only the product under consideration. SGEs invited to participate in the meetings are required to report any personal or imputed financial interests in these products and their sponsors or application holders. Under the law (18 U.S.C. 208(a)), the financial interests of the SGE's spouse, minor children, general partner, organizations in which the SGE is serving as an officer, director, trustee, general partner, employee, as well as prospective employers, impute to the SGE. Any reported interests are assessed to determine whether a disqualifying financial

interest or the appearance of a conflict exists. Where such a disqualifying financial interest exists, the Agency may grant a waiver allowing participation if the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved and the individual's service is necessary to afford the committee essential expertise.

FDA screens advisory committee members broadly for covered relationships that could present even the appearance that they have conflicts of interest that could affect their impartiality. *See* 5 CFR 2635.502. In addition, ODAC members may be excluded for participation as the principal investigator for a key efficacy study for the product under consideration or other perceived conflicts.

CDER notes that the NCCN receives financial support from Genentech for distribution of independently developed content,<sup>56</sup> and 9 of the 27 members of the Breast Cancer Panel — *one-third* of the members — have received financial support from Genentech.<sup>57</sup>

Although CDER recognizes the expertise of the NCCN Panels, CDER considers the extensive expertise in general medical oncology and in the management of breast cancer and extensive qualifications in clinical trial design and evaluation held by the standing members of the ODAC more than sufficient for them to provide scientifically qualified and medically relevant advice to FDA. ODAC members are also educated in the regulatory standards for approval, are provided with more detailed information regarding clinical trial design, conduct, and results supporting new claims, and are more carefully screened for potential conflicts than

---

<sup>56</sup> *See* [http://www.nccn.org/about/financial\\_support.asp?p=about](http://www.nccn.org/about/financial_support.asp?p=about). The NCCN “recognizes that the majority of NCCN Guidelines Panel Members have complex relationships with industry[.]” *See* <http://www.nccn.org/about/disclosure.asp>.

<sup>57</sup> NCCN Guidelines Version 2.2011 Panel Members Breast Cancer; Breast Cancer Panel Financial Disclosures List at [http://www.nccn.org/disclosures/panel\\_list.asp?ID=53](http://www.nccn.org/disclosures/panel_list.asp?ID=53). Includes clinical research support or compensation for service on Advisory Board, Speaker's Bureau, Expert Witness, or Consultant.

NCCN Panel members. Therefore, CDER finds that the NCCN Panel is, on balance, less qualified than the ODAC to provide advice on this specific regulatory issue.

**F. The New Information That Genentech Cites Does Not Alter the Risk-Benefit Balance of Avastin for MBC**

Genentech contends that data from four new studies support that Avastin has a favorable risk-benefit ratio because “subsequent data from independent studies with the Avastin and paclitaxel combination are consistent with the PFS results observed in E2100”. Specifically, Genentech cites the median duration of PFS reported for patients receiving Avastin and paclitaxel in two uncontrolled studies<sup>58,59</sup> and two randomized, controlled studies.<sup>60,61</sup> CDER has not reviewed or confirmed the integrity of the underlying data for any of these studies, and the only publicly available data for three of the four studies are abstracts.

The studies have limitations with regard to design (i.e., single-arm trial) or comparison to unapproved controls (ixabepilone for first-line therapy or motesanib), and the controlled studies have limited sample sizes with large confidence intervals around the estimated median PFS. PFS data in single-arm trials are not interpretable because the trial design does not isolate the contribution of the treatment from the natural history of the disease, which is, in turn, contingent

---

<sup>58</sup> 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.

<sup>59</sup> 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.

<sup>60</sup> 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.

<sup>61</sup> 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.

on the prognostic and baseline characteristics of the population enrolled. For this reason, FDA guidance states that randomized trials are essential for assessing time-to-event endpoints, including PFS.<sup>62</sup> Similarly, ICH E9 *Statistical Principles for Clinical Trials*, a guidance adopted by the international pharmaceutical community and regulatory agencies, states that randomization provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects.

CDER also notes that for the two studies with internal controls available for comparison, Genentech has failed to point out that neither of these studies shows an effect size that is of similar magnitude to that of E2100. In the sole randomized study that isolates the contribution of Avastin to paclitaxel (CIRG-TORI 010 trial), the difference in median PFS between the Avastin and paclitaxel combination and paclitaxel alone is 2.5 months (9.0 vs. 11.5 months) and the difference in overall response rates was 10.1% (41.5% vs. 51.6%). Neither of these findings comes close to the magnitude of the treatment effect in E2100. Rather, these results are similar to the reported treatment effects identified in AVADO and RIBBON1. In randomized, active-controlled studies of Avastin plus paclitaxel as the active control against investigational agents under investigation for use in combination with paclitaxel for the first-line treatment of MBC (ixebepilone alone or sunitinib plus paclitaxel),<sup>63</sup> the differences of magnitude between treatment arms was similarly small, with differences in median PFS of 1.6 (ixebepilone) or 1.8 months (sunitinib plus paclitaxel).

---

<sup>62</sup> Guidance for industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007), see Appendix 5.

<sup>63</sup> <http://clinicaltrials.gov/ct2/show/results/NCT0037325>.

Based on this limited information, these additional trials do not verify the magnitude of the treatment effect on PFS shown in the E2100 trial and, in CDER's view, do not support a finding that the benefits of Avastin outweigh the risks when used to treat patients with MBC.

## **VII. CONCLUSION**

At its core, the subject of the Avastin hearing is straightforward. The hearing must focus on whether the two required confirmatory clinical trials for Avastin verified clinical benefit and whether Avastin is safe and effective for the approved MBC indication. CDER has exercised its sound scientific judgment and has determined that this is not the case. The confirmatory trials failed to verify clinical benefit and that the totality of the evidence before CDER demonstrates Avastin is not safe or effective for first-line treatment of MBC. The arguments put forward by Genentech do not show CDER's findings to be erroneous and are aimed primarily at distracting attention from these core issues. Consistent with the relevant statutory and regulatory framework, CDER has determined that withdrawal of Avastin's MBC indication is necessary and is in the public interest.

## Appendices

1. Federal Register Vol. 57, No. 73. Accelerated Approval. Proposed Rule. 1992.
2. Federal Register Vol. 57, No. 239. Accelerated Approval. Final Rule. 1992.
3. House of Representatives Report 105-310 (1997)
4. FDA Guidance for Industry: Available Therapy (July 2004)
5. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007)
6. Avastin Approval Letter for Metastatic Carcinoma of the Colon and Rectum (February 26, 2004)
7. Regulatory History of Avastin's MBC Indication
8. Common Toxicity Criteria (CTC) Version 2.0, April 30, 1999
9. Genentech Response to the Notice of Opportunity for a Hearing (January 16, 2011)
10. December 5, 2007 ODAC:
  - Agenda
  - Committee Roster
  - Meeting Roster
  - Briefing
  - Final Questions
  - Slides: FDA (Cortazar), FDA (Pai-Scherf), and Genentech
  - Final Minutes
  - Transcript
11. CDER's review of the efficacy supplement BL STN 125085\91 (E2100 and AVF0776g)
  - Office Director
  - Division Director
  - Clinical
  - Statistics
12. Genentech letter requesting FDA review of STN125085\91 under the regulations pertaining to 21 CFR 601.40, Subpart E - Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses (February 15, 2008)

13. Genentech letter requesting FDA review of STN125085\91 under the regulations pertaining to 21 CFR 601.40, Subpart E - Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses (February 20, 2008)
14. Common Terminology Criteria for Adverse Events (CTCAE) v3.0, August 9, 2006
15. CDER's Review of the sBLA STN125085\191 (AVADO)
  - Division Director
  - Clinical
  - Statistics
16. CDER's Review of the sBLA STN125085\192 (RIBBON1)
  - Division Director
  - Clinical
  - Statistics
17. Tabular Summary of Treatment Effects on PFS and Overall Survival
18. July 20, 2010 ODAC:
  - Agenda
  - Committee Roster
  - Meeting Roster
  - Briefing
  - Final Questions
  - Slides: FDA and Genentech
  - Final Minutes
  - Transcript
19. CDER's Review of sBLA STN125085/205 (RIBBON2)
  - Division Director
  - Clinical
  - Statistics
20. Kaplan-Meier Survival Curves for Overall Survival:
  - E2100 Trial - Overall Survival Avastin plus Paclitaxel vs. Paclitaxel
  - AVADO Trial - Overall Survival Avastin 7.5 mg/kg plus Docetaxel vs. Placebo plus Docetaxel
  - AVADO Trial Overall Survival Avastin 15.0 mg/kg plus Docetaxel vs. Placebo plus Docetaxel
  - RIBBON1 Trial - Overall Survival Avastin plus Taxane or Anthracycline vs. Placebo or Taxane or Anthracycline
  - RIBBON 1 - Pre-Specified Overall Survival Subgroup Analysis Avastin plus Taxane vs. Placebo plus Taxane

- RIBBON 1 - Overall Survival Avastin plus Capecitabine vs. Placebo plus Capecitabine
- AVF2119g Trial - Overall Survival Avastin plus Capecitabine vs. Capecitabine
- RIBBON2 Trial - Overall Survival Avastin plus Chemotherapy vs. Placebo plus Chemotherapy

21. Office Director Memo Supporting the NOOH (December 15, 2010)
22. October 28, 2004 Teleconference Minutes
23. Type B Meeting Minutes (January 10, 2006)
24. Type B pre-sBLA Meeting Minutes (February 26, 2009)
25. EMEA Guideline on the Scientific Application and the Practical Arrangements Necessary to Implement Commission Regulation (EC) No 507/2006 on the Conditional Marketing Authorisation for Medicinal Products for Human Use Falling Within the Scope of Regulation (EC) No 726/2004 (December 2006) (p. 40)
26. Genentech slides summarizing high level results from the AVADO trial, including the final PFS and the interim Overall Survival results
27. AVADO Complete Response Letter (December 16, 2010)
28. RIBBON1 Complete Response Letter (December 16, 2010)
29. RIBBON2 Complete Response Letter (December 16, 2010)
30. Notice of Opportunity for a Hearing (December 16, 2010)
31. Type B pre-sBLA Meeting Minutes (October 7, 2008)
32. Type B pre-sBLA Meeting Minutes (March 2, 2010)
33. Letter to NCI (May 10, 2002)
34. FDA-Approved Label for Avastin (2/8/2011)
35. FDA Guidance for Industry: Patient-Reported Outcome Measures – Use in Medical Product Development to Support Labeling Claims (December 2009)

## References

- Dagher, R., Johnson, J., Williams, G., Keegan, P., Pazdur, R. Accelerated Approval of Oncology Products: A Decade of Experience. *JNCI*. 2004; 96: 1500-1509.
- Genmari A, Stockler M, Puntoni M, et al. "Duration of Chemotherapy for Metastatic Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Clinical Trials" *J Clin Oncol*: 2011 April 4 (e-pub ahead of print).
- Heffner AC, Milbrandt EB, Venkatamaran R, Trials stopped early for benefit? Not so fast! *Critical Care*. 11:305, 2007.
- Ioannidis JP, Contradicted and Initially Stronger Effects in Highly Cited Clinical Research. *JAMA*. 294: 218-228, 2005.
- Johnson, J., Ning, YM, Farrell, A., Justice, R., Keegan, P., Pazdur, R. Accelerated Approval of Oncology Products: The Food and Drug Administration Experience. *JNCI*. 2011; 103: 636-644.
- Mackey J, Hurvitz S, Crown J, et al. CIRC-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.
- Montori VM, Devereaux PJ, Adhikari NKJ, et al., Randomized Trials Stopped Early for Benefit: A Systematic Review. *JAMA* 294: 2203-2209, 2005.
- Pocock SJ and Hughes MD, Practical Problems in Interim Analyses, with Particular Regard to Estimation. *Controlled Clinical Trials* 10: 209S-221S, 1989.
- 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.
- 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.