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

Post-Hearing Submission Supporting CDER's Proposal to Withdraw Approval of Avastin's Indication for the Treatment of Metastatic Breast Cancer

Docket No. FDA-2010-N-0621

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INTRODUCTION

In February 2008, the Center for Drug Evaluation and Research ("CDER") granted Avastin (bevacizumab) accelerated approval for use in combination with paclitaxel to treat HER2-negative metastatic breast cancer ("MBC") patients who have not previously received chemotherapy for MBC.[1] Avastin is also FDA-approved for colorectal, lung, kidney, and brain cancers. Avastin's MBC approval was based on one clinical trial, E2100, which showed an increase in median progression-free survival ("PFS") of 5.5 months for patients receiving Avastin plus chemotherapy compared to chemotherapy alone, with no increase in overall survival or improvement in health-related quality of life. Based on these results, CDER determined that accelerated approval was appropriate, with a requirement that Genentech conduct post-approval trials to confirm the magnitude of PFS seen in E2100 or to demonstrate some other clinical benefit in patients, such as an increase in overall survival or improvement in health-related quality of life.

Genentech selected AVADO and RIBBON1, both of which were ongoing at the time CDER granted accelerated approval, as its confirmatory trials. The differences in median PFS between the Avastin-containing treatment arms compared to the control arms in these studies were less than one month in both of AVADO's treatment arms, 1.2 months in RIBBON1's anthracycline/taxane cohort, and 2.9 months in RIBBON1's capecitabine cohort. Neither AVADO nor RIBBON1 showed an improvement in overall survival or health-related quality of life, and both failed to confirm the magnitude of PFS seen in E2100. Two other trials submitted by Genentech, AVF2119g and RIBBON2, demonstrated differences in median PFS between the Avastin-containing treatment and control arms of 0.7 months and 2.1 months, respectively, in

[1] Although there is no cure for MBC, there are safe and effective treatment options available, including first-line treatments. *See* Referenced Back-Up Slides, 2010-FDA-N-0621-0360 ("CDER's Back-Up Slides") at 5.

MBC patients who had failed prior therapy. These trials also failed to confirm the magnitude of PFS seen in E2100, and showed no improvement in overall survival.

The totality of the data on Avastin for MBC indicates that the PFS effect seen in the E2100 trial was an outlier. That magnitude of effect has not been confirmed in subsequent trials. Avastin's minimal effect on PFS, in the absence of an increase in overall survival or an improvement in patient quality of life, does not outweigh the drug's substantial and life-threatening toxicities, which include gastrointestinal ("GI") perforation and fistula, wound healing complications, hypertension, left ventricular dysfunction, proteinuria, and hemorrhage. Because the confirmatory trials failed to verify the magnitude of the PFS effect seen in E2100, and because the totality of the evidence demonstrates that Avastin has not been shown to be safe and effective for MBC treatment, CDER proposed to withdraw Avastin's MBC indication.[2]

Genentech requested a hearing on the proposed withdrawal of Avastin's MBC indication. CDER and Genentech made submissions to the docket setting forth their positions on the proposed withdrawal.[3] FDA held a two-day public hearing on the proposal, which consisted of public comments; affirmative presentations by each party followed by questioning from the other party; questioning, discussion, and voting by the Oncologic Drugs Advisory Committee ("ODAC"); and questioning by Dr. Karen Midthun, the Presiding Officer.[4] The ODAC carefully

[2] *See* Proposal To Withdraw Marketing Approval; Notice of Opportunity for a Hearing for the Breast Cancer Indication for Bevacizumab (Avastin), 12/16/10, FDA-2010-N-0621-0001 ("NOOH").
[3] *See* Submission of Genentech, Inc. in Response to [FDA's] Notice of Opportunity for a Hearing and Proposal to Withdraw Approval of AVASTIN® (Bevacizumab) in Combination with Weekly Paclitaxel for the First-Line Treatment of Patients with [MBC], 1/16/11, FDA-2010-N-0621-0014 ("GT's NOOH Resp."); Joint Statement of Undisputed Facts and Select Issues in Dispute of the FDA Center for Drug Evaluation and Research and Genentech, Inc., 4/7/11, FDA-2010-N-0621-0132 ("Jt. Stmt."); Summary of Arguments Supporting CDER's Proposal to Withdraw Approval of Avastin's Indication for the Treatment of MBC, 5/13/11, FDA-2010-N-0621-0144 ("CDER's Sum. of Arg."); Pre-Hearing Summary of Evidence and Arguments of Genentech, Inc. in Support of Maintaining the Accelerated Approval of AVASTIN® (Bevacizumab) in Combination with Paclitaxel for the First-Line Treatment of HER2-Negative Metastatic Breast Cancer, 5/13/11, FDA-2010-N-0621-0146 ("GT's Pre-Hearing Sum.").
[4] *See* Hearing Transcript, 6/28/11, FDA-2010-N-0621-0429 ("6/28 Trans."); Hearing Transcript, 6/29/11, FDA-2010-N-0621-0429 ("6/29 Trans.").

considered each question raised in this matter and, at the close of the hearing, unanimously agreed with CDER's proposal.[5] Specifically, the ODAC agreed with CDER that the confirmatory trials failed to verify Avastin's clinical benefit for the MBC indication, that no available evidence shows an effect that outweighs Avastin's risks for MBC, and that FDA should not maintain Avastin's accelerated approval for MBC while Genentech designs and conducts additional trials intended to verify the drug's clinical benefit.

Withdrawal of Avastin's MBC indication is the correct outcome here. Genentech argues that the legal standard for withdrawal has not been met, but that if the Commissioner finds that the withdrawal standard has been met, then the Agency should exercise its discretion to continue Avastin's MBC approval while the firm conducts yet another trial to try to demonstrate clinical benefit. By Genentech's own projections, however, the company's proposed trial would not be completed until at least 2016, and the trial may not, in fact, be feasible to complete. Moreover, all available data suggest that the new trial is no more likely to substantiate Avastin's clinical benefit for MBC than the three completed post-approval trials. Continuing approval of this indication under these circumstances would be inconsistent with the public health objectives of the accelerated approval program. For these reasons, as well as the reasons set forth by CDER in its submissions and during the hearing, Avastin's MBC indication should be withdrawn.

I. Legal Standard for Withdrawal

The Federal Food, Drug, and Cosmetic Act ("FDCA") and its regulations provide that the Agency may withdraw a drug's accelerated approval when, among other things, post-approval trials fail to confirm the drug's clinical benefit or the drug is not shown to be safe or effective,[6] both of which are the case here. Genentech argues that withdrawal of accelerated approval is not

[5] *See* Voting Results from Advisory Committee Members at Hearing on June 29, 2011, FDA-2010-N00621-0421 ("ODAC Votes").
[6] 21 U.S.C. § 356(b)(3)(B) and (C); 21 C.F.R. § 601.43(a)(1) and (6).

appropriate unless there is: (1) "*no* reasonable likelihood [that the drug has] clinical benefit;" and (2) "*no* possibility that additional study might further characterize any potential benefit."[7] In so arguing, Genentech has turned the withdrawal standard on its head, attempting to create a new standard that is inconsistent with the purposes of the accelerated approval program and that impermissibly imposes on CDER the burden of proving that Avastin can never be shown to be effective in treating MBC.

Avastin's MBC indication was approved under the statutory and regulatory provisions that permit accelerated approval based on adequate and well-controlled clinical trials establishing that the product has an effect on a clinical endpoint other than survival or irreversible morbidity.[8] It appears that Genentech derived its novel withdrawal standard by conflating a different approval provision—one that permits CDER to grant accelerated approval based on a drug's effect on a surrogate endpoint that is "reasonably likely to predict clinical benefit"[9]—with the *withdrawal* standard. But that provision refers only to the relationship between a surrogate endpoint and clinical benefit, and only as grounds for *approval*. As noted, the MBC indication was not approved based on Avastin's effect on a surrogate endpoint, and its withdrawal does not depend on whether CDER can prove the absence of "reasonable likelihood" of clinical benefit.[10] To the contrary, when the accelerated approval program was created, the Agency was clear that

[7] GT's Pre-Hearing Sum. at 22 (emphases added); *see also* GT's NOOH Resp. at 17 ("Withdrawal is appropriate only where the underlying standard for accelerated approval is no longer met—that is, there is no longer a reasonable likelihood of clinical benefit and there is no meaningful potential for additional study to further characterize that benefit further.").
[8] *See* NOOH at 1-2.
[9] 21 U.S.C. § 356(b)(1); 21 C.F.R. § 601.41.
[10] Moreover, even if Avastin's accelerated approval were based on its effect on a surrogate endpoint, the standard set forth by Genentech is not the appropriate withdrawal standard.

the *sponsor* "has the responsibility for providing the needed evidence confirming clinical benefit."[11] This standard parallels the standard for regular approval of a drug.[12]

Genentech's proposed legal standard impermissibly imposes a burden on CDER to show that there is "no possibility" that an additional trial "might" further characterize the potential benefit of a drug. Requiring CDER to establish that there is no possibility of clinical benefit would be inconsistent with the Agency's approval standards, which place the burden of demonstrating safety and efficacy upon the sponsor, and would be virtually impossible as a practical matter. Another trial of any drug almost always will provide more information about that drug, and there is always the *possibility* that another trial might have a different result. These realities are not grounds to "evergreen" accelerated approval.

Throughout this proceeding, Genentech has stated that the purpose of the accelerated approval program is to provide patients with serious and life-threatening diseases promising new therapies as soon as possible. CDER agrees that this is one important public health purpose of the program. That is why the statute and regulations authorize the Agency to grant accelerated approval based on data showing an effect on an endpoint other than survival or irreversible morbidity, as was done for Avastin's MBC indication. But this is not the only purpose of the program. The other compelling public health purpose underlying accelerated approval—and one that Genentech has consistently neglected to mention—is the interest in protecting patients from

[11] Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58941, 58956 (Dec. 11, 1992).

[12] *See* 21 U.S.C. § 355(b) and (d) (to obtain FDA approval of a new drug application, the sponsor must demonstrate, to FDA's satisfaction, that the drug is both safe and effective for each of its claimed uses); *see also Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 151 (3rd Cir. 1986) ("The Act requires drug manufacturers to show not only that the drug is safe but also to show by 'substantial evidence' that the submitted drug 'will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested.'") (quoting 21 U.S.C. § 355(d)(5)); *Ubiotica Corp. v. FDA*, 427 F.2d 376, 378 (6th Cir. 1970) ("Congress clearly placed on the applicant the burden of establishing that the drug proposed to be distributed in interstate commerce is both safe and effective for the intended use.").

drugs that are unsafe or ineffective or both.[13] That is why the statute and regulations include a process for accelerated withdrawal: to safeguard against the risk that patients are exposed to a drug for which clinical benefit is not verified in post-approval trials, or for which the risks outweigh the benefits. If the withdrawal standard were re-written as Genentech advocates, it would upset the balance of public health interests that the accelerated approval program was meant to strike: providing patients with promising new therapies, while also protecting them from drugs that are unsafe or ineffective.

As explained below, Genentech's post-approval trials failed to confirm Avastin's clinical benefit for MBC, and Avastin's serious risks exceed the demonstrated effects on PFS for the treatment of MBC. Therefore, the legal standard for withdrawal of Avastin's MBC indication has been met.

II. Post-Approval Trials Fail to Verify Avastin's Clinical Benefit for MBC

The first question under consideration is whether the AVADO and RIBBON1 trials fail to verify Avastin's clinical benefit for the approved MBC indication. The answer to this question, as confirmed by the ODAC during the hearing, is ***YES***.[14]

The following facts are not disputed: (1) the AVADO trial showed differences in median PFS of 0.8 months [hazard ratio ("HR") of 0.70 (95% confidence interval ("CI"): 0.55, 0.90), p=0.005] for the 7.5 mg/kg dosage, and 0.9 months [HR of 0.62 (95% CI: 0.48, 0.79) p<0.0003]

[13] "If the agency is not able to withdraw approval rapidly in the event it loses the assurances regarding demonstration of actual clinical benefit [], then the agency believes that, under the authority of [21 U.S.C. § 355(d)], the drug cannot on an ongoing basis meet the standards of safety and efficacy required for marketing under the [FDCA]. Otherwise, the risk of continued exposure of patients with serious or life-threatening diseases to ineffective or unsafe drugs outweighs the potential benefits." Proposed Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 13234, 13239 (Apr. 15, 1992).

[14] *See* ODAC Votes at 1-2; *see also* 6/29 Trans. at 227-30.

for the 15 mg/kg dosage;[15] (2) the RIBBON1 trial showed differences in median PFS of 1.2 months [HR of 0.64 (95% CI 0.52, 0.80), p<0.0001] in the anthracycline/taxane cohort, and 2.9 months [HR of 0.69 (95% CI 0.56, 0.84), p<0.0002] in the capecitabine cohort;[16] (3) Avastin's post-approval trials showed a difference in median PFS of a lesser magnitude than the 5.5 month increase in median PFS seen in the E2100 trial;[17] (4) no clinical trials have shown an increase in overall survival[18] or improvement in health-related quality of life with Avastin's use;[19] (5) the safety data observed in the E2100, AVADO, and RIBBON1 trials were consistent with the safety profile of Avastin described in its approved prescribing information, which includes a Genentech agreed-upon Boxed Warning[20] listing the drug's known increased risks of serious and life-threatening safety problems including GI perforation, surgery and wound healing complications, and hemorrhage;[21] and (6) the other known serious adverse effects of Avastin include hypertension, proteinuria (abnormal amounts of protein in urine), fistula formation, and arterial thromboembolic events, such as myocardial and cerebral infarction.[22]

The totality of the available data fails to verify Avastin's clinical benefit for the treatment of MBC.

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[15] *See* Jt. Stmt. at 4 ¶ 19 and Attachment ("Att.") 2; *see also* Final - CDER Avastin Presentation, FDA-2010-N-0621-0359 ("CDER's Slides") at 49. There was a typographical error in CDER's Sum. of Arg. at 22, which listed the upper bound of the 95% confidence interval for AVADO's 15 mg/kg dosage as 0.70 instead of 0.79.

[16] *See* Jt. Stmt. at 4 ¶ 19 and Att. 2; *see also* CDER's Slides at 67. There was a typographical error in CDER's Sum. of Arg. at 24, which listed the p value for the capecitabine cohort as <0.0001 instead of <0.0002.

[17] *See* 6/29 Trans. at 9 (Genentech admits that subsequent studies of Avastin "demonstrate a [PFS] benefit but of a lesser magnitude" than E2100).

[18] *See* 6/29 Trans. at 143-44 ("DR. JENKINS: So you would agree with the statement that there is no demonstrated overall survival advantage for Avastin in first-line metastatic breast cancer? DR. REIMANN: Yes.").

[19] *See* 6/29 Trans. at 171 (Genentech's Dr. Horning admitted: "[W]e do not have quality of life data that meet CDER's standards from our first-line metastatic breast cancer trials."); *see also* Jt. Stmt. at Att. 1 (Avastin's Full Prescribing Information states: "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.").

[20] A Boxed Warning is the most drastic way that FDA communicates serious adverse effects to physicians. *See* 6/29 Trans. at 142 ("DR. JENKINS: And did Genentech agree to this boxed warning language, or did FDA order you to implement this language for the safety risk? DR. HORNING: We agreed.").

[21] *See* Jt. Stmt. at 5 ¶ 23 and Att. 1.

[22] *Id.*

A. AVADO and RIBBON1 Failed to Verify the PFS Effect Seen in E2100

Progression-free survival ("PFS"), the primary endpoint in Avastin's MBC clinical trials, refers to the time from the start of treatment until disease progression or death from any cause and is determined primarily by evaluating radiographic scans to determine whether tumors are growing.[23] An effect on PFS does not necessarily mean that a patient's life will be extended or her quality of life will be improved.[24] As CDER has consistently advised Genentech,[25] CDER determines whether a PFS improvement represents a clinical benefit by looking at the magnitude of the effect in assessing the benefit-risk profile of the drug.[26]

Genentech claims that because AVADO and RIBBON1 "met their prespecified primary endpoints," they "do not invalidate the findings of E2100."[27] However, as discussed in Section I *supra.,* the applicable standard is not whether the Agency can establish that confirmatory studies "invalidate" the initial study data. Rather, the accelerated approval process requires the *sponsor* to provide data from confirmatory trials that "*verify*" clinical benefit.[28] That is far different than requiring *CDER* to show that the confirmatory trials "*invalidate*" the trial upon which accelerated approval was based.

The parties agree that the degree of improvement in median PFS observed in the E2100 trial (5.5 months [HR of 0.48]) was, at the time of Avastin's 2008 approval for its MBC indication and in the context of its safety profile, considered by CDER to represent a clinical

[23] 6/28 Trans. at 130-31.
[24] *Id.* at 131; *see also* CDER's Sum. of Arg. at 1, 8.
[25] *See e.g.,* 6/28 Trans. at 174-76.
[26] *See* Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf, at 3, attached at Exhibit ("Ex.") 1; *see also* CDER's Sum. of Arg. at 8.
[27] 6/29 Trans. at 8; *see also id.* at 34-35, 77-78.
[28] *See* 21 C.F.R. § 601.41 ("Approval under this section will be subject to the requirement that the applicant study the biological product further, to *verify* and describe its clinical benefit . . . .").

benefit for MBC patients.[29] The parties also agree that the magnitude of PFS effect seen in E2100 has not been confirmed by subsequent trials.[30] Nonetheless, Genentech contends that AVADO and RIBBON1 verify Avastin's clinical benefit for MBC because: (1) the overall PFS results in these trials were statistically significant; (2) CDER's focus on differences in median PFS as the primary method of assessing magnitude of treatment effects "appears to represent a change in CDER's thinking since 2008" and is flawed; and (3) the PFS hazard ratios from AVADO and RIBBON1 show that "a highly statistically significant and clinically meaningful effect is present in both studies."[31] Genentech is wrong on all scores.

First, statistical significance is not the same as clinical benefit. Indeed, when asked by the ODAC's Dr. Balis whether Genentech thought that finding a statistically significant difference equates to a clinically significant outcome, Genentech's Dr. Reimann responded "no" and Genentech's Dr. Barron responded, "There's no question that you can have a statistically significant effect that's not clinically meaningful."[32] The fact that AVADO and RIBBON1 had statistically significant overall PFS outcomes does not establish that these trials verify that Avastin provides clinical benefit.[33]

Second, CDER does not, in fact, focus primarily on differences in median PFS to assess magnitude of effect, and CDER's attention to differences in median PFS is neither novel nor flawed. CDER has consistently used median time-to-event values to provide a temporal context for judging the clinical relevance of the hazard ratio; it is an accepted convention in describing

[29] Jt. Stmt. at 4 ¶ 16.
[30] *See e.g.,* 6/29 Trans. at 40 ("Genentech knew that the results with docetaxel plus Avastin in AVADO had not replicated the magnitude of median PFS seen in E2100."), 90 ("AVADO and RIBBON 1 met their PFS endpoints, but with a lesser magnitude of effect for Avastin with non-paclitaxel chemotherapy.").
[31] 6/29 Trans. at 12, 13, 43.
[32] 6/29 Trans. at 159, 162.
[33] *See Warner Lambert,* 787 F.2d at 154-56 ("Given the strength of the congressional concern with the protection to the public underlying the Drug Amendments of 1962, it would be anomalous to hold that drug manufacturers may demonstrate effectiveness merely by showing statistical significance.").

clinical trial results for time-to-event comparisons such as the PFS endpoint.[34] As noted at the hearing, Genentech's own advertising for Avastin's MBC indication prominently characterized E2100's treatment effect by highlighting the difference in median PFS for each arm.[35] Accordingly, Genentech has no basis on which to discredit CDER's use of differences in median PFS.

Third, reliance on hazard ratios alone, as Genentech seems to be urging, is misleading and inappropriate, because such analysis fails to capture the temporal relation between two trial arms, an important way of viewing hazard ratios in perspective.[36] As CDER biostatistician Dr. Sridhara explained during the hearing, "[A] change in two months to four months versus a change in 12 months to 24 months, under certain assumptions, you can say that the hazard ratio is .5 in both cases. So in order to understand [ ] the temporal implication of this, we do look at both [the hazard ratio and the median PFS]."[37] Dr. Sridhara further explained, "we have had applications where the hazard ratio was .5 and, in fact, the difference in PFS was just two weeks. . . . [T]he hazard ratio was small enough, but the difference in medians was too small to be clinically meaningful."[38] Genentech conceded this point when CDER's Dr. Jenkins asked: "So how can I put a hazard ratio into perspective without looking at the magnitude of the median

[34] 6/28 Trans. at 178-79; *see also* Guidance for Industry, Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, January 2006, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127534.pdf, at 8, attached at Ex. 2 ("When presenting differences between study group and comparator, it is important to present the absolute difference between treatment groups for the endpoint measured, as well as the relative difference (e.g., relative risk reduction or hazard ratio). . . . In most cases, the treatment effect is presented as a mean or median result accompanied by a measure of uncertainty or distribution of results for the treated groups.").
[35] 6/28 Trans. at 179; *see also* CDER's Slides at 97.
[36] 6/28 Trans. at 242-44.
[37] *Id.* at 242.
[38] *Id.* at 243.

difference in progression-free survival?" and Genentech's Dr. Reimann responded, "You can't. You need to look both at hazard ratios and absolute benefits."[39]

Genentech's argument that the hazard ratios in AVADO and RIBBON1 verified *clinical benefit* is incorrect and should be rejected. When considering the differences in median PFS and the hazard ratios in AVADO and RIBBON1, it is clear that these trials failed to verify the magnitude of the treatment effect on PFS seen in E2100, or any other benefit.

B. RIBBON2 Failed to Verify the PFS Effect Seen in E2100

In addition to AVADO and RIBBON1, CDER carefully reviewed the results of the RIBBON2 trial, a randomized placebo-controlled trial of various chemotherapy agents (i.e., taxane, gemcitabine, vinorelbine, and capecitabine) in combination with Avastin or placebo in previously treated HER2-negative MBC patients.[40] Genentech sought to expand Avastin's MBC indication based on RIBBON2 to include patients who had received prior chemotherapy for use of Avastin in combination with a taxane, capecitabine, or gemcitabine.[41] But RIBBON2 showed a difference in median PFS of only 2.1 months [HR of 0.78 (95% CI: 0.64, 0.93) p=0.0072], well below the median 5.5 month difference seen in E2100, and no overall survival benefit.[42] Thus, RIBBON2 also failed to confirm the magnitude of PFS seen in E2100.

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Based on the three post-approval trials submitted by Genentech—AVADO, RIBBON1, and RIBBON2—CDER concluded that the PFS results from E2100 were an outlier that overestimate Avastin's effect. No trial of Avastin for MBC has confirmed the magnitude of PFS effect observed in the E2100 trial that led CDER to grant accelerated approval, and no trial has

[39] 6/29 Trans. at 140.
[40] 6/28 Trans. at 168; CDER's Sum. of Arg. at 30-31 n.35.
[41] 6/28 Trans. at 168.
[42] *Id.*; *see also* CDER's Slides at 78.

demonstrated either an increase in overall survival or an improvement in health-related quality of life. In light of the significant risks associated with Avastin, the benefit-risk profile of this drug for MBC is unfavorable.[43]

As explained further below, based on the totality of the available evidence, Avastin's treatment effects can no longer be viewed as outweighing the drug's risks for patients with MBC.

III. The Totality of the Available Evidence Fails to Demonstrate that Avastin is Safe and Effective for the Treatment of Metastatic Breast Cancer

The next questions to be decided are whether the available evidence fails to demonstrate that Avastin is (1) effective and (2) safe for the approved MBC indication. The answers to these questions are ***YES***, as confirmed by the ODAC.[44]

A. Avastin's Efficacy for its Approved MBC Indication Has Not Been Confirmed

No clinical trial has shown that Avastin increases overall survival or improves health-related quality of life.[45] Only the E2100 trial has suggested a PFS difference of a magnitude sufficient to outweigh the drug's serious risks. Four other clinical trials, AVF2119g (a trial conducted in the second- and third-line setting[46] prior to approval), AVADO, RIBBON1, and RIBBON2, have not verified the magnitude of the PFS difference seen in E2100. Genentech nonetheless argues that the MBC indication should be maintained because the data establish a "reasonable likelihood of clinical benefit."[47] But Avastin's serious and life-threatening risks far outweigh any demonstrated effect in the treatment of MBC, and the MBC indication should be withdrawn.

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[43] *See* 6/29 Trans. at 218 (ODAC's Dr. Freedman: "If the efficacy changes and turns out to be not as much as was thought of originally, then the risk-benefit ratio must change. Then there may be less tolerance for the degree of toxicity or the severity of the toxicity.").
[44] ODAC Votes at 3-6; *see also* 6/29 Trans. at 235-38, 244-47.
[45] *See* 6/29 Trans. at 143-44, 171.
[46] "Second-line treatment" is treatment for a disease or condition after the initial treatment (first-line treatment) has failed. "Third-line treatment" is treatment for a disease or condition after the first-line and second-line treatments have failed.
[47] GT's NOOH Resp. at 15-18.

At the time CDER granted Avastin accelerated approval for MBC, CDER had reviewed the final data from only two clinical trials: AVF2119g, which failed to meet its primary endpoint of PFS in the treatment of second- and third-line MBC; and E2100, which showed a 5.5 month difference in median PFS in the treatment of first-line MBC, with no increase in overall survival or improvement in health-related quality of life.[48]

Now, CDER has the complete results of three additional post-marketing clinical trials, AVADO, RIBBON1, and RIBBON2, for a total of nearly 2,400 MBC patients in whom the risks and benefits of Avastin added to chemotherapy were evaluated. As discussed in Section II *supra.* and below, these trials demonstrate much smaller PFS differences than were seen in E2100, and no effect on overall survival or health-related quality of life. E2100 must be viewed in light of these other trials, and when so viewed, it is clear that E2100 is an outlier.[49] Because Avastin has been shown to have only a modest effect in treating MBC, there is no justification for continuing to expose patients to the serious risks associated with its use.

B. Avastin Has Known Serious and Life-Threatening Risks

As noted previously, CDER and Genentech agree that the safety data observed in the E2100, AVADO, and RIBBON1 trials are consistent with the safety profile of Avastin described in its approved prescribing information.[50] Specifically, Avastin carries a Boxed Warning because of its known serious and life-threatening toxicities, which include GI perforations, wound healing complications, and hemorrhage.[51] Moreover, there were Avastin-related deaths in each clinical trial, including in E2100, and the addition of Avastin to chemotherapy resulted in

[48] CDER also looked at top-line AVADO results, in the form of 22 slides, but only to confirm that AVADO was not a failed trial. *See* 6/28 Trans. at 177, 258-59. Those slides showed a 0.8 month difference in median PFS and a trend—highlighted by Genentech with a red circle on the relevant slide—towards improvement in overall survival. CDER's Slides at 95; *see also* 6/28 Trans. at 177-78; 6/29 Trans. at 39, 120-22.
[49] *See* CDER's Slides at 100 (bar graph of the absolute difference in PFS in all trials).
[50] *See* footnote 21, *supra.*
[51] *Id.*

an overall increase in serious adverse events ("SAEs") and grade 3-5 adverse events ("AEs").[52] Yet Genentech now suggests that Avastin is not a highly toxic drug[53] and has "generally manageable" side effects.[54] Genentech's attempt to minimize the risks associated with Avastin's use is not supported by the evidence.

1. Avastin-Related Deaths

CDER carefully reviewed the available data from the E2100, AVADO, and RIBBON1 trials and concluded that deaths attributable to Avastin were observed in approximately 0.8 to 1.7% of the breast cancer patients enrolled in the trials.[55] Although CDER agrees with Genentech that death attribution is difficult and subjective,[56] CDER's attribution of deaths to Avastin is fair, indeed, conservative, because only deaths to severe toxicities known to be associated with Avastin have been attributed to Avastin. As Dr. Pai-Scherf explained at the hearing:

> There are cases -- and one case here that we have a patient who developed wound healing complications and fistula and died a few weeks later and was attributed as causes other than to Avastin. So death attribution is difficult, and being a reviewer with this product for almost six years, I see many cases coming to my desk. And my

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[52] *See* CDER's Slides at 50, 65, 73, 83. The term "serious adverse event" is short-hand for "serious adverse drug experience," which is defined as an adverse drug experience that:

> (A) results in--(i) death; (ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form); (iii) inpatient hospitalization or prolongation of existing hospitalization; (iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or (v) a congenital anomaly or birth defect; or (B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).

21 U.S.C. § 355-1(b)(4). The severity of AEs in the clinical trials at issue here were graded using the National Cancer Institute's ("NCI") Common Terminology Criteria for AEs ("CTCAE"), v.2, available at http://ctep.cancer.gov/ protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf and v.3.0 (Aug. 9, 2006), FDA-2010-N-0621-0145, Appendix 14. "The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild AE; Grade 2 Moderate AE; Grade 3 Severe AE; Grade 4 Life-threatening or disabling AE; Grade 5 Death related to AE." FDA-2010-N-0621-0145, Appendix 14 at 1.

[53] *See* 6/29 Trans. at 10 (people are left with the "inaccurate perception that Avastin is a toxic drug"), 18 ("Avastin has been unfairly characterized by CDER as a very toxic drug.").

[54] GT's Pre-Hearing Sum. at 10, 11, 20; *see also* 6/29 Trans. at 18, 19, 84, 101, 153, 200.

[55] *See* CDER's Sum of Arg. at 3, 16 (E2100 = 1.7%), 22-23 (AVADO = .8%), 24-25 (RIBBON1 = 1.2%).

[56] 6/29 Trans. at 21.

> overall feeling is that the 1 percent attribution is a conservative number of deaths attributed to Avastin.[57]

The number at the high end of CDER's estimate, 1.7%, comes directly from Avastin's prescribing information, which was based solely on the E2100 trial and accepted by Genentech: "Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin. Causes of death were GI perforation (2), myocardial infarction (2), diarrhea/abdominal, and pain/weakness/hypotension (2)."[58]

The number at the low end of CDER's estimate, 0.8%, comes from the AVADO trial, in which CDER attributed two deaths, out of 247 patients who received Avastin at the 15 mg/kg dose, to known toxicities of Avastin.[59] Specifically, CDER attributed to Avastin one death due to pulmonary hemorrhage and one death due to GI perforation, as these are known toxicities of Avastin and not generally associated with the chemotherapy partner drug.[60]

Between the high and low estimates is 1.2%, which represents a total of ten Avastin-related deaths in the RIBBON1 trial, as follows: five deaths, out of 413 patients who received Avastin in the anthracycline/taxane cohort, due to GI perforation/bleeding (4) and pulmonary hemorrhage (1);[61] and five deaths, out of 404 patients who received Avastin in the capecitabine

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[57] 6/28 Trans. at 227.

[58] *See* Jt. Stmt. at 5 ¶ 22 and Att. 1; 6/29 Trans. at 22 ("[Genentech] agreed to and ha[s] used CDER's E2100 analysis in our product label and in our pooled incidence figures."); *see also* CDER's Slides at 27.

[59] 6/28 Trans. at 155; CDER's Slides at 46; CDER's Back-Up Slides at 2.

[60] *See* FDA-2010-N-0621-0460 ("Sealed AEs"), Att. 1 at 28-29, Att. 3 at 25-26, Att. 4 at 24-25 (ID 7351 - massive haemoptysis (i.e., pulmonary hemorrhage)); Att. 1 at 3-4, Att. 3 at 3-4, Att. 4 at 3-4 (ID 1506 - suspected GI perforation). Like CDER, the clinical trial investigators concluded that these two deaths were probably due to Avastin.

[61] *See* CDER's Slides at 64. The clinical trial investigators concluded that four of these deaths were probably related to Avastin. *See* Sealed AEs, Att. 5 at 10-11, Att. 6 at 9-10 (ID 32806 - bowel perforation); Att. 5 at 43-44, Att. 6 at 49-52 (ID 45001 - abdominal abscess); Att. 5 at 21-22, Att. 6 at 21-23 (ID 36355 - perforated ileal ulcer) (all GI perforations); Att. 5 at 44-45, Att. 6 at 52-55 (ID 45102 - pulmonary hemorrhage). In the fifth case, the clinical trial investigator concluded that the patient's GI bleeding was related to Avastin, but the investigator did not report the cause of the patient's GI hemorrhage. *See* Sealed AEs, Att. 5 at 128-29, Att. 6 at 151-53 (ID 41304).

cohort, due to myocardial infarction (2), cardiac failure (2), and cardiac arrest (1).[62] In the anthracycline/taxane cohort, CDER determined that the five deaths were attributable to Avastin because they resulted from known toxicities of Avastin, not toxicities generally associated with the chemotherapy partner. For the capecitabine cohort, CDER attributed to Avastin five deaths due to cardiac events because, although capecitabine may be associated with an increased risk of cardiac events, there were no cardiac deaths in the capecitabine control arm and arterial thromboembolic events, such as myocardial infarction and left ventricular dysfunction that led to these deaths, are well known toxic events associated with Avastin.[63]

Genentech disagrees with CDER's attribution of deaths to Avastin and cites a pooled death rate analysis of the E2100, AVADO (15 mg/kg dosage), and RIBBON1 trials,[64] noting that "there were fewer total deaths, fewer MBC deaths, and a similar rate of non-breast cancer deaths in the E2100 study and also in the pooled safety analysis for standard dose Avastin plus chemotherapy."[65] Although CDER does not dispute the number of deaths cited by Genentech, CDER does dispute the propriety of the pooling methodology used by Genentech. It is inappropriate and misleading to compare death rates, because of the differing lengths of follow-up among patients and across trials, as well as differing treatment arm allocation ratios (i.e., proportion of patients receiving Avastin) across studies. The statistically appropriate way to compare deaths in this case would be to compare overall survival curves using a log-rank test,

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[62] *See* CDER's Slides at 72. There was a typographical error in slide 72, which should have noted two deaths due to cardiac failure. *See* Dr. Pai-Scherf's Clinical Review STN125085\192 ("RIBBON1 Clin. Rev.") at 56-57, found in FDA-2010-N-0621-0145, Appendix 16. In the case narratives provided by Genentech for these AEs, the clinical study investigators concluded that the AEs were *not* related to Avastin. *See* Sealed AEs, Att. 5 at 28-29, Att. 6 at 27-28 (ID 39101 - cardiac failure); Att. 5 at 36-37, Att. 6 at 41-42 (ID 42203 - myocardial infarction); Att. 5 at 29-30, Att. 6 at 29-30 (ID 40302 - cardiac arrest); Att. 5 at 56-58, Att. 6 at 65-66 (ID 48952 - myocardial infarction); Att. 5 at 47-48, Att. 6 at 55-57 (ID 46008 - cardiac failure).
[63] 6/28 Trans. at 163, 166-67; *see also* CDER's Slides at 64, 72-73; RIBBON1 Clin. Rev. at 56-57.
[64] 6/29 Trans. at 20; *see also* Genentech Inc. - Testimony, 2010-FDA-N-0621-0424 ("GT's Slides") at 26-27.
[65] 6/29 Trans. at 24-25.

which accounts for differing follow-up times and when done properly, does not demonstrate an improvement in overall survival by adding Avastin in all trials.[66]

Genentech also argues that CDER's classification of Avastin-related deaths is "bias[ed]" and "imbalanced," because CDER allegedly "defined a subset of treatment-related deaths as Avastin-related according to specific AE terms which have been associated with Avastin," but "the terms were applied only to the Avastin arms, even though these same adverse events also occurred with chemotherapy alone."[67] Genentech misconstrues CDER's analysis, which was unbiased and balanced.

Contrary to Genentech's contentions, CDER looked at all of the deaths on study, including the deaths in the chemotherapy-only arms.[68] CDER does not dispute that all toxicities known to be associated with Avastin can also occur in the general population and in the oncology population receiving chemotherapy, and that certain AEs were seen in both the chemotherapy-only arms and the Avastin arms.[69] However, the data show that such AEs occur more frequently and are more serious in the Avastin-treated population.[70]

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[66] *See* E2100 Statistical Review and Evaluation, found in FDA-2010-N-0621-0145, Appendix 11, 88-115, at 14 and Table 5; AVADO Statistical Review and Evaluation, FDA-2010-N-0621-0156, at 27-28 and Table 15; RIBBON1 Statistical Review and Evaluation, found in FDA-2010-N-0621-0145, Appendix 16, 118-140, at 14 and Table 8 (anthracycline/taxane cohort), 18 and Table 13 (capecitabine cohort). *See also* FDA Briefing Document ODAC Meeting, July 20, 2010, found in FDA-2010-N-0621-0145, Appendix 18, 8-34, at 27 (Table 10).

[67] *Id.* at 21-24.

[68] *See, e.g.*, CDER slides at 46-48 (AVADO), 61 (RIBBON1 anthracycline/taxane cohort), 72 (RIBBON1 capecitabine cohort). *See also* Dr. Pai-Scherf's Clinical Review STN125085\191 ("AVADO Clin. Rev."), found in FDA-2010-N-0621-0145, Appendix 15, 34-105, at 52 ("All case report forms and narratives for patients who died on study were reviewed."), 56-57; RIBBON1 Clin. Rev. at 54 ("Pertinent case report forms and narratives were all reviewed."), 54-57; Dr. Pai-Scherf's Clinical Review STN125085\91 ("E2100 Clin. Rev."), found in FDA-2010-N-0621-0145, Appendix 11, 24-87, at 50-54 (tables showing narratives for paclitaxel only and paclitaxel plus Avastin arms).

[69] *See, e.g.*, CDER slides at 46-48 (AVADO), 61 (RIBBON1 anthracycline/taxane cohort), 72 (RIBBON1 capecitabine cohort).

[70] *See id.* at 27 (20.2% increase in grade 3-5 toxicity in E2100), 44-50 (increase in SAEs and grade 3-5 AEs in AVADO), 61-65, 71-73 (increased incidence of SAEs and grade 3-5 AEs; increased incidence of AEs attributed to Avastin in both of RIBBON1's cohorts).

When CDER attributes an AE or death to a drug, it looks at all of the information available regarding the event and takes into consideration the following factors, among others: (1) the temporal relationship of the AE or death to the drug; (2) the biological plausibility that the AE or death was caused by the drug; (3) the likely other possible causes of the AE or death; and (4) other similar events that are known to have occurred with the drug (e.g., AEs listed on drug's label).[71] Here, CDER looked at, among other things, the case narrative reports submitted by Genentech for deaths other than disease progression, SAEs, grade 3-5 AEs, and AEs leading to drug discontinuation.[72] There were examples in which the same AEs occurred in both the chemotherapy-only and Avastin arms of a trial, but where CDER did not attribute the AEs to Avastin, because they could have been caused by the chemotherapy.[73] And there were other examples where CDER did attribute to Avastin certain AEs that also happened to appear in the chemotherapy-only arm of the trial, because the AE appeared in Avastin's Boxed Warning and occurred with greater severity in the Avastin-containing arm.[74]

CDER's analysis properly considered deaths in both the Avastin-containing and chemotherapy only arms of the clinical trials. Accordingly, CDER's attribution of deaths was fair and balanced.

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[71] *See generally* NCI Guidelines For Investigators: Adverse Event Reporting Requirements (July 26, 2011), available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf, attached at Ex. 3; Guideline for Industry Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A (March 1995), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073087.pdf, attached at Ex. 4; Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (April 1996), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf, attached at Ex. 5.

[72] *See generally* Sealed AEs.

[73] *Compare, e.g.,* Sealed AEs, Att. 5 at 42, Att. 6 at 48-49 (ID 44702 - sepsis in taxane subgroup placebo arm) *with* Att. 5 at 52-53, Att. 6 at 59-60 (ID 48208); Att. 5 at 54-55, Att. 6 at 60-63 (ID 48402) (both sepsis in taxane subgroup Avastin arm).

[74] *Compare, e.g.,* Sealed AEs, Att. 1 at 83-84, Att. 4 at 76-78 (ID 2003 - GI perforation - appendix) and Att. 1 at 268-69, Att. 4 at 249-51 (ID 7201 - GI perforation - bowel) (both in docetaxel-only arm) *with* Att. 1 at 3-4 , Att. 3 at 3-4, Att. 4 at 3-4 (ID 1506 - fatal suspected GI perforation); Att. 1 at 187-88, Att. 3 at 83-84, Att. 4 at 173-74 (ID 4504 - GI perforation - large intestine) (both in Avastin arm). Notably, the clinical trial investigators also concluded that patient ID 1506's death and patient ID 4504's SAE were probably due to Avastin.

2. Avastin Causes Other Toxic Adverse Events

Avastin is also associated with more common toxicities, including minor bleeding (manifesting as epistaxis), hypertension, proteinuria, and an increased incidence of chemotherapy-related toxicities such as neutropenia, febrile neutropenia, sensory neuropathy, diarrhea, and hand-foot syndrome.[75] As noted, all clinical trials submitted by Genentech have showed an increase in SAEs and grade 3-5 AEs with Avastin's use.[76] Indeed, Avastin's label lists the adverse events for the MBC indication as follows:

> Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in [E2100]. Grade 3-4 adverse events occurring at a higher incidence (≥ 2%) in 363 patients receiving paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%), bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3% vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/desquamation (3% vs. 0.3%) and proteinuria (3% vs. 0%).
>
> Sensory neuropathy, hypertension, and fatigue were reported at a ≥ 5% higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.[77]

Despite the risk of Avastin-related deaths, serious adverse events, and common adverse events, Genentech minimizes Avastin's toxicity, arguing that "Avastin has been unfairly characterized by CDER as a very toxic drug,"[78] and that "Avastin has serious side effects, as described in the product label, but it is not more or uniquely toxic compared to other MBC treatments."[79] However, because Avastin is used in combination with chemotherapy, Avastin's serious toxicities are added to the known toxicities associated with chemotherapy. Thus, in exchange for little to no additional treatment effect on PFS, patients are subjected to both

[75] 6/28 Trans. at 191; Jt. Stmt. at 5 ¶ 22 and Att. 1.
[76] *See* footnote 70, *supra.*
[77] Jt. Stmt. at Att. 1.
[78] 6/29 Trans. at 18.
[79] *Id.* at 34.

Avastin's unique toxicities and to an increased incidence of the toxicities shared by Avastin and its chemotherapy partner.

Genentech also argues that the most common adverse events associated with Avastin—hypertension and proteinuria—are "clinically manageable."[80] Numerous public commenters at the hearing also expressed the view that it is easy to manage certain Avastin adverse events such as hypertension and proteinuria.[81] As the ODAC's patient representative Dr. Compagni-Portis explained:

> We have heard reportedly that the risks involved are usual, and that they're manageable, and even that they're similar to other drugs that are given for metastatic breast cancer, but it seems to me that the adverse effects of Avastin are significant, and the studies do show this; that the risks even include death without any demonstrated benefit. Again, I know we've heard from those who say that the symptoms are tolerable, but as Dr. Sekeres pointed out, those anecdotes are not evidence. And so I think that the risks are considerable, and that we shouldn't minimize those risks; that they are very important and that we're not hearing from patients who have really suffered because of the drug.[82]

Despite Genentech's protestations to the contrary, Avastin is a toxic drug. Avastin's modest activity in tumors is not enough to justify its serious and life-threatening risks for MBC treatment.[83]

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[80] GT's Pre-Hearing Sum. at 10, 11, 20; *see also* 6/29 Trans. at 18, 19, 84, 101, 153, 200.

[81] *See e.g.*, 6/28 Trans. at 43, 60-61, 113, and 120.

[82] 6/29 Trans. at 242; *see also* 6/28 Trans. at 83 (Public commenter: "I would like to say that for every woman here testifying, there are other women who we know -- a member of our group who bled out of every orifice of her body, . . . another woman . . . who had a brain hemorrhage. So those people don't come to testify. I just want you to remember that they exist, too"), 197 (CDER's Dr. Keegan: "[T]here are other voices that need to be heard. Those voices include a 53-year-old woman with [MBC] who suffered severe abdominal pain caused by gastrointestinal perforation that led to her death after 4 doses of Avastin; or an asymptomatic 33 year-old woman with treatment-naive [MBC] who suffered a massive fatal pulmonary hemorrhage after 11 doses of Avastin.").

[83] The ODAC's Dr. Wilson made this point:

> If a drug had no side effects but I could not determine any real meaningful clinical benefit, in my view, that drug should not be given to somebody. That is not the case here. In this case, we have a totality of data, [two] confirmatory trials, that while different people may look at them differently, I think reasonable people would agree that a month or so prolongation in progression free [survival] is not really a meaningfully beneficial endpoint . . . . And, yet, we all have heard that the side effects of the Avastin in these trials are similar to those that have been described in the package insert and in the black box warning, which while different from chemotherapy can be very, very serious and lead to acute death.

6/29 Trans. at 242-43.

IV. FDA Should Not Continue Approval While Genentech Conducts Additional Trials

It is clear that the legal standard for withdrawal of Avastin's MBC indication has been met. Withdrawal is the right public health decision. FDA should not continue the approval of Avastin's MBC indication while Genentech conducts additional research to attempt to verify the drug's clinical benefit. Genentech's proposed new clinical trial may not even be feasible, and if feasible, it will not be completed until at least 2016. And Genentech's proposed new trial may fail, because there is no available data to support Genentech's hypotheses that the chemotherapy partner influences Avastin's treatment effect and that there is a subset of women whose MBC may benefit from Avastin. No labeling change or communication to doctors and patients is appropriate where, as here, the data show that Avastin is not safe and effective for MBC treatment. Withdrawal of Avastin's MBC indication is necessary and appropriate.

A. Genentech's Proposed New Trial Will Not Be Completed Until at Least 2016 and May Fail

At the hearing, Genentech stated that it does not plan to *begin* accruing patients for its proposed new trial of Avastin for MBC until the first quarter of 2012.[84] The trial is not projected to be complete until at least 2016,[85] and it may not be feasible at all.[86] The trial contemplates a "futility boundary" after which the firm says withdrawal would be appropriate if the treatment effect is not confirmed; however, the interim analysis to identify the futility boundary will not be reached until three and a half years after the trial begins,[87] i.e., until the end of 2015, shortly before the trial is scheduled to be complete. To permit Avastin to remain approved for MBC for five more years in the face of the data from five adequate and well-controlled trials supporting withdrawal is not in the interest of public health. Moreover, the study may take longer than

[84] 6/29 Trans. at 67.
[85] *Id.* at 133-34.
[86] *Id.* at 66 ("A more detailed feasibility assessment is ongoing.").
[87] *Id.*.

Genentech projects, in part because it may be difficult to recruit subjects in the U.S., because they may be reluctant to agree to participate in a trial in which they might be randomized to not receive an approved treatment.[88] And as explained below, if conducted, the trial may, like the post-approval trials to date, fail to verify the magnitude of PFS treatment effect seen in E2100.

B. Available Data Do Not Support the Existence of a Subgroup of Women for Whom Avastin's Benefit-Risk Analysis is Favorable

Genentech also argues that Avastin's MBC indication should not be withdrawn because there is a subset of women for whom Avastin provides a clinical benefit, but this hypothesis is not supported by the data.[89] As noted previously, CDER has reviewed five adequate and well-controlled trials of Avastin in MBC, which included seven independently powered comparison arms[90] and more than 3,500 patients.[91] Yet the data from these trials do not support Genentech's hypothesis that there is a subgroup of women for whom Avastin works particularly well and for whom the drug's benefits would outweigh its risks.[92]

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[88] *Id.* at 113-14; *see also id.* at 247-48 (ODAC's Dr. Wilson: "One of the reasons in the postmarketing trials that are done following accelerated approval, that the clinical trials are not done in the exact same setting, is because it is very difficult to get patients to agree to be randomized to a therapy that has had at least accelerated approval, making the conduct of those trials very, very difficult. . . . It seems to me that it will be extremely difficult to accrue to such a trial in the United States and Europe…").

[89] A number of MBC patients and their family members spoke of Avastin being effective in the treatment of MBC. In addition to that testimony being anecdotal, it was clear from the comments that many of these patients were not taking Avastin for the approved indication at issue here, which is for use in combination with paclictaxel to treat HER2 negative MBC patients who have not previously received chemotherapy for MBC. *See e.g.*, 6/28 Trans. at 36 ("I am a triple negative metastatic breast cancer patient who has been on Avastin with Xeloda [capecitabine], not paclitaxel, for 32 months"), 42-43 (I'm a triple negative metastatic breast cancer patient who underwent 40 rounds of chemotherapy. My disease was stable on a regimen of carboplatin and Taxotere over a two-plus-year period. Avastin was added in July of '06."), 56 (patient was treated with "a triple chemo cocktail and Avastin" and "continue[s] to be treated with Avastin as maintenance"), 72 (after her breast cancer metastasized to her lungs, she "immediately began chemotherapy to try to shrink [the tumors]." She "tried two different types of chemotherapy, but the tumors were growing, not shrinking." Now, she has "infusion of Avastin every three weeks and take[s] a Tarceva pill daily . . . .)."

[90] *Id.* at 180.

[91] *Id.* at 207.

[92] *See* 6/29 Trans. at 258 ("There are not, for the most part, differences between the treatment effects in patients who are HER2-negative, ER-, PR-positive, and in those who are triple negative. So we don't have any sense that they respond differently than the other."); *see also* Office Director Memo Supporting the NOOH, FDA-2010-N-0621-0145, Appendix 21, 2-10 ("Office Dir. Mem.") at 5 ("While it is possible that some patients may receive clinical benefit from Avastin for treatment of breast cancer, the available data are not sufficient to demonstrate that such a subgroup exists and, if so, how to identify the patients in advance.").

Genentech's expert Dr. O'Shaughnessy suggested multiple times at the hearing that "triple negative" patients who have hormone receptor negative disease[93] might be one such subgroup.[94] However, the only data she presented to support this speculation were from the E2100 trial; these findings were not confirmed in subsequent trials.[95] CDER analyzed the E2100, AVADO, and RIBBON1 trials, looking at each independently powered cohort within each trial and separating the triple negative patients from other patients who were HER2-negative and ER or PR-positive.[96] CDER found there were no differences in terms of treatment effects between triple negative patients and others with respect to either overall survival or PFS.[97]

Dr. O'Shaugnessy also suggested that patients with "rapidly progressive symptomatic or heavily tumor-burdened metastatic breast cancer" are a subgroup that receives clinical benefit with Avastin.[98] However, there is no way to know whether women with more symptomatic disease will benefit more than others, because baseline information about symptoms was not collected in the clinical trials.[99] In fact, based on Eastern Cooperative Oncology Group ("ECOG") performance status, one would conclude that all patients in the three trials were either asymptomatic or minimally symptomatic at the time they entered the trials.[100] Thus, as CDER's Dr. Keegan noted, there are "no data on whether or not symptomatic patients would benefit or to what degree they would benefit because they were not studied."[101] In addition, Genentech's

[93] *See* 6/29 Trans. at 16 (describing three types of HER-2 negative breast cancer, including "triple negative.").
[94] *Id*. at 80, 83-84, 86, 261-62; GT's Slides at 105-06, 114.
[95] 6/29 Trans. at 261-62.
[96] *See id.* at 258-59.
[97] *Id.* at 258-59; CDER's Back-Up Slides at 10-11.
[98] 6/29 Trans. at 83.
[99] *Id.* at 257-58.
[100] 6/28 Trans. at 170.
[101] 6/29 Trans. at 257-58.

proposed additional trial is not designed to test whether this subset of patients would respond well to Avastin in the manner hoped for by Genentech.[102]

Another theory advanced by Genentech is that the subgroup of MBC patients with high plasma levels of certain forms of Vascular Endothelial Growth Factor ("VEGF"), particularly VEGF-A, "may be more likely" to benefit from Avastin.[103] The company proposes to explore this hypothesis in the "biomarker component" of its proposed study.[104] CDER does not dismiss this hypothesis or the merits of studying it. However, the underlying science is very preliminary, and largely based on exploratory, retrospective analyses with mixed results.[105] A scientific theory about whether it is possible to identify a subgroup of MBC patients that may benefit from Avastin based on a biomarker is not a reason to maintain approval in light of the known and certain risks of harm for all.

As ODAC member Dr. Sekeres aptly noted at the hearing:

> We have tried to slice this pie in a lot of different ways to try to find some kind of benefit for this drug in combination with chemotherapy for a desperate breast cancer population. And no matter which way we look at it, [at] what were supposed to be confirmatory studies in progression-free survival, looking at toxicity, looking at overall survival, looking for data about subgroups, all we're left with are crumbs.

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[102] *See generally* January 21, 2011 Pre-Meeting Package and February 22, 2011 Type B Meeting Minutes, filed *under seal* on August 4, 2011 ("Sealed Proposed Biomarker Study Docs.").
[103] GT's NOOH Resp. at 63; *see generally* Sealed Proposed Biomarker Study Docs.
[104] GT's NOOH Resp. at 63; *see generally* Sealed Proposed Biomarker Study Docs.
[105] For example, there was no correlation between tumor tissue VEGF expression levels and outcomes in the subset of patients for whom tissue samples were available from the E2100 trial, the trial upon which Genentech's "continued approval" argument rests. *See* Schneider BP, *et al.*, *Association of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor-2 Genetic Polymorphisms With Outcome in a Trial of Paclitaxel Compared With Paclitaxel Plus Bevacizumab in Advanced Breast Cancer: ECOG 2100,* 26:4672-4678, 4675, J. Clin. Oncol. (2008), available at http://jco.ascopubs.org/content/26/28/4672.full.pdf, attached at Ex. 6. There was also no observed predictive effect of VEGF-A in retrospective subset analyses of available archival tumor tissue from patients in the AVF2119g trial. Jubb, *et al.*, *Impact of Exploratory Biomarkers on the Treatment Effect of Bevacizumab in Metastatic Breast Cancer*, 17:372-381, 376, 379, Cancer Clinical Research (2011), available at http://clincancerres.aacrjournals.org/content/17/2/372, attached at Ex. 7. A study of baseline plasma VEGF levels of patients in the AVADO study showed that high VEGF levels were associated with larger PFS effects, but the available abstract, cited by Genentech, provides only hazard ratios. GT's NOOH Resp. at 63 (citing Miles DW, *et al.*, *Plasma biomarker analyses in the AVADO Phase III Randomized Study of First-Line Bevacizumab + Docetaxel in Patients with Human Epidermal Growth Factor Receptor (HER) 2-Negative Metastatic Breast Cancer* (Dec. 10, 2010), available at http://www.abstracts2view.com/sabcs10/ view.php?nu=SABCS10L_939&terms, attached at Ex. 8.).

> There's nothing we can hang our hat on in these studies that would make me feel comfortable continuing to expose a lot of patients to risk without a clear benefit.[106]

There are simply no available data to support Genentech's theory that there is a subgroup of women for whom Avastin's benefit-risk analysis may be favorable.

C. Genentech's Chemotherapy Partner Hypothesis is Not Supported

Genentech also argues that the magnitude of the treatment effect seen with Avastin in combination with chemotherapy will be influenced by the specific chemotherapy partner used.[107] According to Genentech, to confirm the benefit seen in E2100, the company should be permitted to conduct a trial in which Avastin is again paired with paclitaxel.

If there were merit to Genentech's chemotherapy partner hypothesis, one would expect to see evidence of drug interactions or antagonism between Avastin and other chemotherapy drugs. There is none.[108] Moreover, Genentech has submitted no data suggesting a synergistic relationship between Avastin and paclitaxel that would lend credence to the idea that Avastin in combination with paclitaxel might work better than the additive effects of paclitaxel or Avastin alone.[109] And Genentech has submitted no data suggesting an antagonistic relationship between Avastin and the other chemotherapy partners paired with Avastin in the AVADO, RIBBON1,

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[106] 6/29 Trans. at 260-61.

[107] GT's Pre-Hearing Sum. at 9, 17-19; 6/29 Trans. at 35, 43-47.

[108] 6/28 Trans. at 182-83:

> [W]e have not been provided with evidence of pharmacokinetic interactions between Avastin and any of the chemotherapeutic agents used in AVADO or RIBBON 1, nor have we been provided with evidence of antagonism between Avastin and any of the chemotherapeutic agents administered in AVADO or RIBBON 1. By antagonism, I mean that the treatment effects of Avastin plus other chemotherapeutic agents, when given in combination, are smaller than the sum of the treatment effects when each drug is given alone.

[109] *Id.* at 182:

> CDER is unaware of and Genentech has not provided this type of scientific data, such as evidence of synergism between Avastin and paclitaxel. By synergism, I mean that the treatment effects of Avastin and paclitaxel given together is larger than the sum of the treatment effects of each drug when that drug is given alone.

See also Office Dir. Mem. at 5 ("Assertions 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.").

and RIBBON2 trials that might have accounted for the much smaller PFS difference seen in those trials. As Dr. Keegan explained at the hearing, "[c]lassic pharmacokinetic study designs have been developed to test such hypotheses, but these tests have not been done, or if performed, have not been submitted to CDER."[110]

To the contrary, existing pharmacokinetic data demonstrate that "there are no interactions between Avastin and any of the chemotherapeutic agents administered with Avastin in the AVADO and the RIBBON 1 studies."[111] In the absence of a scientifically supported basis for chemotherapy-specific interactions, 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.

Additionally, CDER reviewed a report published online in The Lancet in March 2011 on the CIRG-TRIO-010 trial—a three-arm, randomized, placebo and active-controlled phase 2 trial—which Genentech referenced in its January 16, 2011 submission[112] and which CDER referred to as "Study 10" at the hearing.[113] Study 10 contained one arm in which paclitaxel was administered alone and one arm in which paclitaxel and Avastin were administered together. The authors of the article provided the results of a comparison between those two arms and concluded that there was no statistically significant increase in median PFS in the Avastin-containing arm compared to paclitaxel alone.[114] Although PFS difference was not a primary endpoint in this trial, Study 10's results certainly do not suggest that another new trial, in which Avastin is yet again paired with paclitaxel, would succeed in demonstrating clinical benefit.

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[110] 6/28 Trans. at 182.
[111] *Id.* at 183; *see also* Attached Exs. 9 (non-squamous non-small cell lung cancer clinical pharmacology ("clin. pharm.") review), 10 (metastatic colorectal clin. pharm./toxicology review), 11 (metastatic renal cell carcinoma clin. pharm. review), 12 (post-marketing commitment clin. pharm. review).
[112] *See* GT's NOOH Resp. at 24 and n.52.
[113] Attached at Ex. 13; *see also* 6/28 Trans. at 185-87, 203. CDER's Slides mistakenly referred to this study as "CIRG-TORI-010" instead of "CIRG-TRIO-010."
[114] *See* 6/28 Trans. at 184-86; *see also* Ex. 13.

Finally, Genentech's proposed trial is not designed to test its "chemotherapy-specific partner" hypothesis.[115]

In light of the foregoing, allowing Avastin's MBC indication to remain approved until at least 2016, when Genentech's proposed trial may be completed, is neither responsible nor in the public interest.

D. A "Middle-Ground" Approach is Inappropriate Here and Would Run Counter to the Intent and Purpose of the Accelerated Approval Program

Genentech has stated that there is a desirable "middle ground" between withdrawing the MBC indication for Avastin and maintaining that approval. For example, Genentech has proposed to modify the labeling to state that the MBC indication is only for use with paclitaxel (and not other chemotherapy agents)[116] and to reflect the current data regarding Avastin use for MBC.[117] Genentech has also stated that it would adopt a Risk Evaluation and Mitigation Strategy ("REMS")[118] consisting of a Medication Guide and a special communication plan to help physicians and patients make informed treatment decisions.[119]

There is no realistic middle ground here. FDA can require a company to develop and implement a REMS to manage serious risks associated with a drug when the agency determines that such a strategy is "necessary to ensure that the benefits of the drug outweigh the risks of the drug."[120] The data here do not demonstrate that Avastin provides a clinical benefit for MBC patients. If a drug does not provide a benefit, no amount of communication, training, or

[115] *Id.* at 188 ("With the exception of the use of a placebo infusion in the control arm, the proposed treatment plan is the same as that used in the E2100 trial.").
[116] Avastin's labeling currently states that "Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel." Jt. Stmt. at Att. 1.
[117] GT's NOOH Resp. at 66-67.
[118] *Id.* A REMS may include training for healthcare providers, restrictions on distribution and access, patient monitoring or documentation of safe use conditions, or other parameters to ensure that a drug is used safely and effectively when safe and effective use is possible. *See* 21 U.S.C. § 355-1(e) and (f).
[119] GT's NOOH Resp. at 67.
[120] 21 U.S.C. § 355-1(a)(2)(A).

distribution restrictions will make that drug safe and effective. Simply stated, there is no REMS that can achieve the goal of ensuring the benefits of Avastin outweigh its risks for MBC.

Permitting Avastin's MBC indication to remain approved with labeling changes and/or a REMS is inappropriate where, as here, the totality of the evidence shows that Avastin for MBC is not safe and effective. Prescription labeling is designed to give prescribers and their patients information about the risks and safe use of a demonstrably effective product; if a drug has not been shown to be effective, any risk is unacceptable.[121] This is all the more true where, as here, the known adverse events associated with Avastin use are serious.[122] In this matter, Genentech is asking that the drug remain approved for the MBC indication, despite its failure to establish that Avastin for MBC is safe and effective. But doing so will provide false hope: leading patients and physicians to believe that Avastin can be safely and effectively used for MBC. Patients and physicians must be able to have confidence that FDA-approved indications are supported by data; the data here simply do not support such labeling. Thus, any middle ground proposal, such as new labeling or restrictions on use, could be as detrimental to the integrity of the accelerated approval program as maintaining approval of Avastin's MBC indication.

In the face of clear and compelling evidence that Avastin for MBC does not provide a clinical benefit to patients and has serious and potentially lethal risks, the integrity of the accelerated approval program necessitates withdrawal of the indication. If approval must be continued so long as a sponsor is willing to conduct additional studies, then the withdrawal standard has no meaning. Accordingly, based on CDER's scientific judgment, supported by the ODAC at two advisory committee meetings before the hearing and at the hearing, and in

[121] As the ODAC's Dr. Wilson explained: "[W]hen I went through medical school, it was always do no harm. If a drug had no side effects but I could not determine any real meaningful clinical benefit, in my view, that drug should not be given to somebody." 6/29 Trans. at 243.
[122] *See* 21 C.F.R. § 201.56(a)(3).

furtherance of the public health, prompt withdrawal of Avastin's MBC indication is necessary and appropriate.

CONCLUSION

Notwithstanding that Avastin's clinical benefit for MBC has not been confirmed in a single clinical trial since CDER granted accelerated approval for the MBC indication based on E2100, and that the totality of the evidence demonstrates that Avastin has not been shown to be safe and effective for first-line treatment of MBC, Genentech asks FDA to suspend its scientific assessment of Avastin for MBC at the time accelerated approval was granted in 2008, to disregard the totality of the scientific evidence amassed since that time, and to allow the company a "do-over" on the unsuccessful trials intended to confirm the results of E2100. Such a result is contrary to the very basis of accelerated approval, which makes approval contingent on completed post-approval trials that verify the drug's clinical benefit, and the bedrock principle that the benefit-risk analysis of a drug evolves over time based on the available data.

Based on the totality of the evidence now available, the statutory and regulatory standard for withdrawal of Avastin's MBC indication has been met. It is not in the interest of the public health to continue Avastin's MBC approval or to permit continued approval for MBC with a REMS or labeling change while Genentech conducts a new trial, especially in light of Genentech's timeframe for its proposed trial and the fact that it is unlikely to confirm Avastin's clinical benefit in treating MBC.

For all of the foregoing reasons, Avastin's MBC indication should be withdrawn.