

DOCKET NO. FDA-2010-N-0621

**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**

Presiding Officer Karen Midthun, M.D. has granted a hearing on the Center for Drug Evaluation and Research's ("CDER's") proposal to withdraw approval of Avastin® (bevacizumab) in combination with paclitaxel for the first-line treatment of HER2-negative metastatic breast cancer ("MBC"). Genentech, Inc. ("Genentech") believes that proposal is contrary to the accelerated approval standards, the science on Avastin, and the public health. For these reasons, Genentech respectfully opposes withdrawal.

In advance of the June 28-29, 2011 hearing on CDER's proposal, Genentech makes this submission (1) describing what the evidence offered at the hearing will establish and (2) summarizing Genentech's arguments in favor of Avastin's continued accelerated approval with paclitaxel for the first-line treatment of HER2-negative MBC subject to a confirmatory study and evaluation of a biomarker for those patients more likely to derive a greater benefit from treatment.¹

¹ On January 17, 2011, Genentech made a submission to FDA identifying the data, analyses, and information on which Genentech intends to rely at the hearing. Genentech incorporates by reference the contents of that submission, including its appendices and attachments.

Introduction

In every first-line MBC study, Avastin has increased progression-free survival (“PFS”), with the greatest effect seen when Avastin was combined with weekly paclitaxel in the E2100 study. The 5.5-month improvement in median PFS in the E2100 study represents the largest incremental benefit in median PFS observed in a first-line MBC trial, and Avastin’s effect on objective response rate was similarly impressive. Based on these data, consensus treatment guidelines and clinicians widely adopted Avastin with paclitaxel as a standard of care for HER2-negative MBC patients, and thousands of women have benefited from Avastin treatment in the three years since its approval.

CDER accepts that the benefit demonstrated with Avastin and paclitaxel in the E2100 study supports approval. Nevertheless, CDER questions the reliability of those findings because the subsequent AVADO and RIBBON1 studies did not show the same extent of PFS benefit when Avastin was combined with other chemotherapies. The core issue presented in this hearing is how to interpret the E2100 dataset: as a reliable indicator of clinical benefit showing that Avastin’s chemotherapy partner affects Avastin’s magnitude of benefit in first-line MBC, or as an unreliable outlier that is not indicative of the true magnitude of Avastin’s effect with paclitaxel.

As described below, Genentech believes E2100 is reliable and that Avastin provides meaningful clinical benefit in an area of serious unmet medical need. Before FDA eliminates access to Avastin as an approved therapeutic option for MBC, Genentech seeks an opportunity to confirm Avastin’s benefit in a trial testing Avastin with weekly paclitaxel. This trial will also evaluate a biomarker for those patients more likely to derive a greater benefit from

treatment. Genentech's proposal is supported by the available data, meets the letter and the spirit of the accelerated approval regulations, and is the appropriate outcome for patients and the public health.

The Evidence

A. Avastin and the Unmet Medical Need in MBC

Breast cancer is the most commonly occurring cancer in women worldwide. In its metastasized form, breast cancer is an aggressive, incurable disease with a relative five-year survival rate estimated to be 23.4%.² In 2010, an estimated 40,000 women in the United States died of MBC. Prognosis is especially poor for patients with HER2-negative disease where hormonal treatment is not viable.

MBC presents unique treatment challenges. As CDER recognizes, "there are not enough effective treatments for this cancer."³ The appropriate treatment strategy depends on multiple patient-specific factors, including tumor burden and related symptoms, underlying tumor biology (including presence or absence of hormone receptors and HER2 status), age and medical co-morbidities, prior treatment in the adjuvant setting, an assessment of the proposed treatment's risks and benefits, and the patient's own treatment goals and wishes.⁴ Due in part to the heterogeneity of MBC, there continues to be "unmet medical need for additional safe and

² National Cancer Institute, Surveillance Epidemiology and End Results, *available at* <http://www.seer.cancer.gov/statfacts/html/breast.html> (last visited 30 April 2011).

³ Letter from Dr. Janet Woodcock to Breast Cancer Community, *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237286.pdf> (last visited 12 May 2011).

⁴ See Joint Statement of Undisputed Facts and Select Issues in Dispute of the FDA Center for Drug Evaluation and Research and Genentech, Inc. ("Joint Statement"), Docket No. FDA-2010-N-0621, ¶ 6 (7 April 2011).

effective therapies for MBC,” a point on which CDER and Genentech agree.⁵ In short, MBC gives rise to exactly the type of serious unmet medical need for which accelerated approval was created.

Avastin responds to this high unmet medical need. When used with traditional chemotherapies, Avastin delays cancer progression and improves response. Significantly, Avastin is the only agent approved specifically for the first-line treatment of HER2-negative MBC. Approximately 70-75% of primary breast cancers are HER2-negative.⁶ In the past 10 years, FDA has approved only one other first-line medication, Gemzar[®] (gemcitabine), that is not limited to HER2-positive patients.⁷

B. Avastin’s Accelerated Approval for MBC Based on the E2100 Study

On February 22, 2008, CDER approved Avastin as a first-line treatment for HER2-negative MBC based on the results of the E2100 study. Because E2100 examined Avastin’s effect only with weekly paclitaxel, CDER limited the MBC approval to that

⁵ *Id.* ¶ 4.

⁶ *Id.* ¶ 7.

⁷ The Presiding Officer’s Notice of Hearing (forwarded May 6, 2011) stated that FDA would not consider during this hearing “issues concerning the consistency of CDER’s position here with CDER’s decisions with respect to other products.” Notice of Hearing at 10. Genentech will of course comply with the Presiding Officer’s determination on this point; however, Genentech respectfully disagrees with this decision on the ground that the appropriateness of an agency’s action may be judged by the consistency of its decisions across similarly-situated regulated parties. *See Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997) (“[A]n agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so.”).

Genentech understands the Presiding Officer’s ruling to preclude Genentech from challenging the consistency of CDER’s regulatory decisions, but not to prohibit the parties—as part of the evaluation of whether Avastin has a favorable benefit-risk profile and addresses an unmet medical need—from discussing how the Avastin safety and efficacy data compare to the data for other MBC treatments. Consideration of Avastin’s place within the existing treatment landscape is consistent with the accelerated approval statute and regulations, as indicated by the various occasions on which CDER and the ODAC have considered other treatment options for first-line MBC in connection with their assessment of Avastin’s benefit-risk. *See, e.g.*, Transcript, July 20, 2010 ODAC at 65, 172-78; Transcript, 5 December 2007 ODAC at 32-37, 223.

chemotherapy, implicitly recognizing that the data might be different for Avastin in combination with other therapies.

The E2100 study was a Phase III randomized trial sponsored by the National Cancer Institute and conducted by the Eastern Cooperative Oncology Group (“ECOG”) in collaboration with nine other cooperative groups. ECOG is one of the largest cancer research organizations in the United States, with a network that includes experienced researchers, physicians, and health care professionals at public and private institutions across the country. The E2100 study enrolled over 700 patients from centers predominantly in the United States; the study’s results thus reflect the demographics, co-morbidities, and standards of care associated with first-line MBC in this country.

In the E2100 study, Avastin with weekly paclitaxel substantially improved median PFS by 5.5 months—from 5.8 to 11.3 months—and reduced the risk of disease progression or death by 52% with a high degree of statistical confidence (HR 0.48, $p < 0.0001$). In addition, the E2100 data showed an improvement in overall survival (“OS”), although not reaching statistical significance (Δ median OS = 1.7 months; HR 0.87, 95% CI 0.72, 1.05, $p = 0.14$)⁸ because the study had only limited power (25% and 38%) to detect an OS increase of three to four months at the median (HR of 0.89 and 0.86, respectively).

At CDER’s request, the results of the E2100 study were subject to rigorous independent confirmatory review. The primary endpoint analysis of the independent radiological facility (“IRF”) was consistent with the assessment of the ECOG investigators (HRs of 0.48 and

⁸ One-year survival improved by 7.4%; 95% CI 1.3%, 13.5%.

0.42, respectively, and a similar prolongation of median PFS), demonstrating no systematic bias. The ECOG dataset results were peer-reviewed and published in the *New England Journal of Medicine*,⁹ and the PFS results from the independent review were published in the *Journal of Clinical Oncology*.¹⁰

Genentech also assessed the issues CDER identified in its review of the E2100 results. That assessment revealed no evidence of bias in the PFS results and a level of data completeness and consistency comparable to the PFS results for other agents that have recently received full approval for MBC treatment, including Tykerb® (lapatinib) and Ixempra® (ixabepilone).¹¹ The E2100 study results were based upon the determination of the study's Data Safety Monitoring Board to release the results at the study's first pre-planned interim analysis with pre-specified allocation of type I error. The amount of PFS information Genentech provided in its submission to CDER resulted in a comparatively high precision in the PFS benefit in the E2100 study, a higher degree of precision than in the other studies of Avastin in first-line MBC. Moreover, the magnitude of PFS benefit observed from the first pre-planned interim analysis was maintained after 21 additional months of follow-up and more than 200 additional PFS events, as published in the *New England Journal of Medicine* based on the ECOG dataset.

⁹ Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *New Engl J Med* 2007;357:2666–76.

¹⁰ Gray M, Bhattacharya S, Bowden C, et al. Independent review of E2100: a Phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 2009;27:4966–72.

¹¹ For example, the concordance rate between investigator and IRF assessments of progression status, 76%, was comparable to the concordance rate observed in the pivotal study for Tykerb that led to its full approval.

CDER granted accelerated approval to Avastin based on its conclusion that “the E2100 trial was statistically robust.”¹² CDER acknowledged that “[t]here was close agreement between investigator-assessed endpoints—both PFS and response rate—and the independent radiographic facility.”¹³ Sensitivity “analyses examining ‘missing data’ did not support the introduction of systematic bias,”¹⁴ and “[m]ultiple sensitivity and subgroup analyses corroborated the drug effect.”¹⁵ In granting accelerated approval, CDER did not identify any new safety issues arising out of the E2100 data, and CDER determined that the data established a positive benefit-risk profile for Avastin with paclitaxel.

C. The AVADO and RIBBON1 Trials

To fulfill the conditions of Avastin’s accelerated approval, Genentech completed two Phase III confirmatory studies in first-line MBC, the AVADO and RIBBON1 studies. The AVADO study tested Avastin’s effect with docetaxel versus docetaxel alone. RIBBON1 consisted of two independently powered comparisons under a single protocol: (1) Avastin and taxane/anthracycline compared with taxane/anthracycline alone (where the taxane was nab-paclitaxel or docetaxel), and (2) Avastin and capecitabine compared with capecitabine alone.

CDER did not establish a specific magnitude of PFS benefit that AVADO and RIBBON1 needed to achieve to confirm the clinical benefit of Avastin in first-line MBC. Rather, CDER advised Genentech only that “the basis for conversion to full approval” would be

¹² “PFS is a Benefit ‘In the Right Context,’ Pazdur Says in Q&A on Avastin Approval,” *The Cancer Letter* 29 February 2008.

¹³ *Id.*

¹⁴ *Id.*

¹⁵ *Id.*

“demonstrated improvement in progression-free survival and evidence that survival is not impaired.”¹⁶ At the time it granted accelerated approval, CDER knew the magnitude of PFS improvement observed in the AVADO study based on a summary of the AVADO data. This summary included the PFS data for the standard Avastin dose of 15 mg/kg, which showed an improvement in median PFS of 0.8 months with an HR of 0.64 (95% CI 0.50, 0.82) (p=0.0003).¹⁷ CDER accepted AVADO as a confirmatory trial for E2100 aware of this result.

AVADO and RIBBON1 met their primary efficacy endpoint of improved PFS with a high degree of statistical significance, although they showed a lesser magnitude of PFS benefit than E2100. Specifically, in the primary analysis of AVADO, there was a 0.9-month median PFS increase and a 38% risk reduction (HR 0.62, 95% CI 0.48, 0.79) (p=0.0003). In a later updated analysis of the AVADO trial performed at the time of the definitive OS analysis, there was a 1.9-month median PFS increase and 33% risk reduction (HR 0.67, 95% CI 0.54, 0.83).¹⁸ In RIBBON1, the taxane/anthracycline comparison showed a 1.2-month increase in median PFS and a 36% risk reduction (HR 0.64, 95% CI 0.52, 0.80) (p<0.0001). RIBBON1’s capecitabine comparison showed a 2.9-month increase in median PFS with a 31% risk reduction (HR 0.69, 95% CI 0.56, 0.84) (p=0.0002).

¹⁶ Minutes, 26 February 2009 Type B Meeting at 7.

¹⁷ Joint Statement, at ¶ 32. The interim OS results were based on data cutoff of 6-months follow-up after the last patient enrolled and showed a stratified HR of 0.65 (0.42, 1.02) (p=0.057). *Id.* As occurred when the interim OS data in E2100 matured, the OS results changed in AVADO when mature data were available. The mature OS data for AVADO at a data cutoff of 24 months after the last patient enrolled (342 events) showed a stratified HR of 1.00 (0.76, 1.32) (p =0.98).

¹⁸ Miles DW, Chan A, Dirix LY, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 2010; 28:3239-47.

Like the E2100 study, neither AVADO nor RIBBON1 was designed to detect an improvement in OS, with less than 11% and 26% power to detect a three- or four-month OS improvement, respectively. Neither AVADO nor the RIBBON1 cohorts showed a significant improvement in OS compared to the chemotherapy arms, and, in aggregate across the first-line studies, no detriment in OS was observed (HR 0.97; 95% CI 0.86, 1.08 in pooled data from E2100, 15 mg/kg AVADO arm, and RIBBON1). Although AVADO and RIBBON1 showed statistically significant improvements in PFS—confirming Avastin’s activity in first-line MBC with multiple chemotherapy partners—the lesser magnitude of PFS benefit observed in those studies with different chemotherapies suggested that Avastin’s benefit may vary by chemotherapy regimen. CDER had previously acknowledged this possibility. At a January 10, 2006 Type B teleconference, CDER recommended that Genentech consider separate studies for different chemotherapies because “the treatment effect *will vary* according to the chemotherapy regimen used,”¹⁹ and CDER limited Avastin’s accelerated approval specifically to use with paclitaxel.

D. Avastin’s Safety Profile

Pooled safety data—from E2100, RIBBON1, and the standard dose arm of AVADO (15 mg/kg)—showed all-cause mortality in the chemotherapy-only arms of the trials was 55.8% versus 52.0% in the Avastin with chemotherapy arms. In that same pooled data, the incidence of death due to adverse event or protocol therapy was identical: 1.8% in the

¹⁹ Joint Statement, at ¶ 25; Minutes, 10 January 2006 Type B Meeting at 2 (emphasis added).

chemotherapy-only and Avastin-chemotherapy arms. The incidence of death due to MBC in the chemotherapy-only arms was 51.5%, versus 48.1% in the Avastin plus chemotherapy arms.

The pooled data from E2100, RIBBON1, and the standard dose AVADO arm showed a 13.3% overall increase in the number of patients experiencing Grade ≥ 3 adverse events for Avastin with chemotherapy relative to chemotherapy alone. Excluding hypertension and proteinuria—both well manageable with established clinical interventions—the increased incidence was 5.6%. Other, more serious events had a relatively low rate of incidence. These events were observed in both the treatment and control arms of the three studies, as follows.

For the Grade ≥ 3 events CDER has highlighted as Avastin toxicities, the incidence rates in the pooled safety data for the Avastin with chemotherapy treatment arms compared to the chemotherapy alone arms were as follows: fistula formation (0.4% vs. 0.3%), gastrointestinal perforation (0.5% vs. 0.3%), venous thromboembolism (“VTE”) (3.0% vs. 3.8%), bleeding (1.6% vs. 0.4%), and arterial thromboembolism (“ATE”) (1.9% vs. 0.3%). The toxicity unique to Avastin was reversible posterior leukoencephalopathy syndrome (“RPLS”). This rare event occurred in only one of the 1,427 patients treated with Avastin, an incidence rate of 0.07%.

These safety data did not change the known safety profile of Avastin. As the Hearing Notice for this proceeding states, “the parties have agreed that the FDA-approved prescribing information for Avastin ‘is a fair and accurate description of the safety profile of Avastin,’ and that ‘[t]he safety data observed in the E2100, AVADO, and RIBBON1 studies were consistent with the safety profile of Avastin described in its approved prescribing

information.”²⁰ That is, CDER and Genentech agree that the E2100, AVADO and RIBBON studies did not identify any new safety signals.²¹

E. Genentech’s Study Proposal

Based on Avastin’s positive effect on PFS, response rates with a range of chemotherapies, and well-established, manageable safety profile, Genentech concluded that AVADO and RIBBON1 confirmed the clinical benefit observed in E2100. Genentech accordingly sought to convert Avastin’s accelerated approval to full approval and to expand Avastin’s MBC indication to a broader range of chemotherapies.

CDER and FDA’s Oncologic Drugs Advisory Committee (“ODAC”) took a different view of the data, concluding that the magnitude of PFS improvement and safety profile in AVADO and RIBBON1 were insufficient to support either full approval or Avastin’s continued accelerated approval for MBC. Genentech responded to ODAC’s views by developing a proposal for a double-blind, randomized, multicenter Phase III study that will further test Avastin’s effect with weekly paclitaxel. This study builds on the observed difference in the magnitude of effect in the paclitaxel E2100 study versus the non-paclitaxel AVADO and RIBBON1 studies, and on the emergence of promising new biomarker data.

Genentech’s proposed Phase III study would include a biomarker component to identify patients likely to derive a more substantial benefit from Avastin. Based on the company’s extensive research, including a new assay sensitive to specific isoforms, plasma concentration of VEGF-A (Avastin’s target) has been identified as a potential predictive

²⁰ 76 Fed. Reg. 27332, 27334 (11 May 2011) (quoting Joint Statement, at ¶¶ 22, 23).

²¹ *Id.*

biomarker in breast, gastric, and pancreatic cancers. In the analysis of MBC patients in the AVADO trial, patients with high levels of VEGF-A had a PFS hazard ratio of 0.49 (with the standard Avastin 15 mg/kg dose) compared with patients with low levels of VEGF-A who had a PFS hazard ratio of 0.87. The data suggest that patients with high VEGF-A levels may be more likely to derive a substantial benefit from Avastin, and it is important and appropriate to validate this predictive biomarker in a prospective Phase III trial.

At a February 22, 2011 Type B meeting on Genentech's study proposal, CDER stated that PFS results confirming the magnitude of treatment effect observed in E2100 without a detriment to OS, coupled with the E2100 data, would support Avastin's full approval with paclitaxel.²² Since that Type B meeting, Genentech has engaged in further study planning activities and intends to submit the protocol under a Special Protocol Assessment.

F. Continued Support for Avastin-Paclitaxel Combination in MBC

Since the July 2010 ODAC meeting, independent expert bodies, including the European Medicines Agency ("EMA"), the National Comprehensive Cancer Network ("NCCN"), and other regulatory authorities, have affirmed Avastin's favorable benefit-risk profile in combination with paclitaxel. Indeed, the Committee on Human Medicinal Products ("CHMP") of the EMA recently provided its expert scientific view that Avastin also has a favorable benefit-risk profile in first-line MBC with capecitabine.²³ The EMA is a highly esteemed sister regulatory authority to FDA, and the NCCN reflects the views of the nation's

²² Minutes, 22 February 2011 Type B Meeting at 5.

²³ See CHMP Post-Authorization Summary of Positive Opinion for Avastin, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000582/WC500105256.pdf (last visited 12 May 2011).

leading cancer centers and breast cancer experts. These views track the treatment decisions of the many clinicians who continue to rely on Avastin as a therapeutic option for appropriate first-line HER2-negative MBC patients.

Comments submitted to FDA following announcement of CDER's withdrawal proposal reveal an even broader range of support for Avastin from a cross-section of stakeholders, including cancer patients; their family and friends; health professionals, including physicians and nurses responsible for the care of cancer patients; and patient advocates.²⁴

Overwhelmingly, these individuals favor Avastin's continued approval for MBC. Of the nearly 350 comments submitted, including a petition containing the signature of over 10,000 individuals, only a single comment supported withdrawal.

The perspectives of leading cancer clinicians and researchers are of particular note. For example, Dr. Julie Gralow of the University of Washington School of Medicine and Seattle Cancer Care Alliance expressed a view held by many leading clinicians:

It is clear that some breast cancer patients derive substantial benefit from Avastin. . . . *To withhold this drug from all patients because some don't benefit is incorrect.* We have lots of cancer agents that are approved for all breast cancer patients that don't result in 100 percent response rates—we don't withhold in all because they only work in an as yet unidentified subset.²⁵

This support among treating oncologists with first-hand insight into Avastin's benefit-risk profile in the clinical setting weighs heavily in favor of continued approval pending further study.

²⁴ Docket No. FDA-2010-N-0621 at Regulations.gov.

²⁵ Comment, Living Beyond Breast Cancer, No. FDA-2010-N-0621-005 (17 December 2010) (emphasis added).

Summary of Argument

In the Notice of Hearing for this matter, the Presiding Officer identified four issues to be considered:

Issue 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?

....

Issue 2A: Does the available evidence on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved?

Issue 2B: 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?

....

Issue 3: If the Commissioner agrees with the grounds for withdrawal set out in issue 1, issue 2A, or issue 2B, 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?

Genentech addresses each of these issues below.

I. Issue 1: Do AVADO and RIBBON1 Fail to Verify Clinical Benefit?

AVADO and RIBBON1 met their primary endpoint of improved PFS with a high degree of statistical significance. For this reason, and for the reasons discussed below, Genentech believes that these studies verified the clinical benefit of Avastin in first-line MBC, and conversely did not refute the clinical benefit observed in the E2100 trial.

Genentech nevertheless recognizes the view of CDER and the ODAC that AVADO and RIBBON1 failed to verify clinical benefit, and Genentech has responded to that

view by limiting its proposal to the maintenance of accelerated approval solely for Avastin and paclitaxel subject to the conduct of an additional study. In light of this response to the views of CDER and the ODAC on this point, Genentech does not intend to focus its hearing presentation on the question of whether AVADO and RIBBON1 verify or fail to verify clinical benefit for Avastin and paclitaxel. Instead, Genentech intends to focus on the question of whether accelerated approval should be maintained for Avastin and paclitaxel subject to a further confirmatory study of this combination, even in light of the views of CDER and the ODAC on AVADO and RIBBON1.

II. Issues 2A and 2B: Avastin's Benefit-Risk Profile Remains Favorable.

The available data show that Avastin consistently improves PFS in first-line MBC, the effect observed for Avastin with paclitaxel in the E2100 study is of a magnitude that CDER accepts as substantial and clinically meaningful, and the safety profile of Avastin is well-characterized and not changed by the findings from E2100, AVADO or RIBBON1.

Withdrawal would thus necessarily rest on a determination that the findings from the E2100 study are no longer reliable and that Avastin presents unique toxicity concerns in the MBC setting. Respectfully, that determination would be contrary to the most reasonable interpretation of the scientific data.

The concerns raised regarding the design and conduct of the E2100 study are belied by the results of the rigorous confirmatory review demonstrating the soundness of the data. The concerns are also inconsistent with CDER's prior positions and actions in approving Avastin based on E2100. Additionally, a definitive conclusion on Avastin's efficacy as a first-line therapy in combination with paclitaxel cannot be drawn based on data reflecting Avastin's

effect with non-paclitaxel chemotherapy and outside the first-line setting. This would depart from CDER's prior recognition that Avastin's effect may vary with chemotherapy partner.

Finally, the view that Avastin presents a distinctly unfavorable safety profile does not appropriately reflect the ability of clinicians to manage Avastin's most common side effects, or the fact that the majority of serious but rare events (including treatment-related deaths) in the first-line MBC studies were seen in both the treatment and chemotherapy-only arms of the studies.

A. Issue 2A: The Data Show a Meaningful Treatment Effect from Avastin with Paclitaxel.

The median PFS benefit of 5.5 months with an HR of 0.48 observed in the E2100 study reflects a significant treatment impact sufficient to support Avastin's accelerated approval in MBC. These findings emerged from a well-designed, scientifically rigorous study conducted by one of the largest cancer research organizations in the world and subject to extensive independent confirmatory review. CDER recognized the soundness of the E2100 data when the agency approved Avastin's MBC indication based on these data. The questions CDER has raised now about the design and conduct of the study are at odds with its prior judgment that sensitivity and subgroup analyses, together with the "close agreement between investigator-assessed endpoints . . . and the independent radiographic facility," supported Avastin's approval for MBC.²⁶

²⁶ PFS Is a Benefit "In the Right Context," Pazdur Says in Q&A on Avastin Approval, The Cancer Letter, 29 Feb. 2008.

Similarly, the lesser magnitude of benefit observed for Avastin in the AVADO and RIBBON1 trials should not be viewed as invalidating the findings for Avastin with paclitaxel in E2100. AVADO and RIBBON1 show Avastin's positive activity in MBC. The observation of a lesser magnitude of benefit in these non-paclitaxel studies suggests that Avastin's PFS effect may vary with chemotherapy partner.

Although the scientific cause for this differential effect has not been definitively resolved, certain core propositions are established: (1) VEGF is a vascular endothelial survival factor, (2) VEGF removal by Avastin sensitizes the tumor vasculature to cytotoxic damage by chemotherapy, (3) anti-VEGF extends the activity of commonly used breast cancer chemotherapies, and (4) while most combinations with chemotherapy demonstrate increased efficacy in preclinical models, anti-VEGF + paclitaxel is particularly active, demonstrating tumor reduction in addition to delaying tumor growth.²⁷

Although taxanes have similar mechanisms of action, they are not necessarily clinically interchangeable. Dose, schedule, and safety issues have led to different outcomes in metastatic and early breast cancer.²⁸ Hence, it is reasonable to infer that the chemotherapy partner could influence the magnitude of overall observed treatment effect across studies. CDER

²⁷ Bagri A., Berry L., et al. Effects of Anti-VEGF Treatment Duration on Tumor Growth, Tumor Regrowth, and Treatment Efficacy. *Clin Cancer Res* 16 (15): 3887-900 (2010).

²⁸ Jones, S.E., Erban, J., et al. Randomized Phase III Study of Docetaxel Compared With Paclitaxel in Metastatic Breast Cancer. *J Clin Oncol*, Vol 23(24), 2005:5542-5551. Gradishar, W.J., Krasnojon, D., et al. Significantly Longer Progression-Free Survival With nab-Paclitaxel Compared With Docetaxel As First-Line Therapy for Metastatic Breast Cancer. *J Clin Oncol* Aug 1, 2009:3611-3619. Harvey, V. Mouridsen, H., et al. Phase III Trial Comparing Three Doses of Docetaxel for Second-Line Treatment of Advanced Breast Cancer *J Clin Oncol* Nov 1, 2006:4963-4970. Gradishar, W.J., Tjulandin, S., et al. Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil-Based Paclitaxel in Women With Breast Cancer *J Clin Oncol* Nov 1, 2005:7794-7803.

itself previously recognized that the “treatment effect [would] vary according to the chemotherapy regimen used.”²⁹ In addition, CDER was already informed of the observed difference in PFS from the AVADO study prior to granting accelerated approval to Avastin in first-line MBC, accepting that the totality of the data reasonably predicted the likelihood of a clinical benefit.

Following the public announcement of the AVADO results, several possible explanations for the observed differential effect of Avastin when added to taxanes emerged.³⁰ One possible explanation relates to the favorable toxicity profile of paclitaxel administered on a weekly schedule, which enables treatment delivery for a longer period before disease progression. In the E2100 study, the Avastin-paclitaxel pairing afforded a 7.3-month median exposure to the cytotoxic and anti-angiogenic properties of the combined agents. By contrast, the median duration of exposure to the Avastin-docetaxel combination was 5.5 months for the standard Avastin dose in the AVADO trial³¹ and 4.2 months in RIBBON1. Of the E2100 patients treated with Avastin and paclitaxel, 33.2% were still on therapy at one year. None of the patients in the AVADO Avastin-docetaxel cohort had a comparable length of exposure, and only 6.3% of the RIBBON1 patients receiving Avastin and docetaxel remained on treatment at one year. Early discontinuations were also more frequent in the AVADO trial than in E2100; the

²⁹ Minutes, 10 January 2006 Type B Meeting at 2.

³⁰ Avastin Breast Cancer Approval In Spotlight With AVADO. The Pink Sheet DAILY, Wednesday May 11, 2011. Nine Members of the Oncology Community Speak Out about Bevacizumab's Role in Metastatic Breast Cancer. ASCO Post September 2010, Volume 1, Issue 4. Bevacizumab for Advanced Breast Cancer: All Tied Up With a RIBBON? (editorial) Harold J. Burstein J Clin Oncol. 2011 Apr 1;29(10):1232-5.

³¹ Per protocol, docetaxel duration was capped at 6.2 months in the AVADO study.

percentage of patients who discontinued the combination of a taxane and Avastin two or more months prior to disease progression was 39% for E2100 compared to 64% for AVADO.

While Genentech acknowledges the risks in cross-trial comparisons, the length of median PFS improvement correlated with duration of combination exposure in the three randomized controlled trials in first-line MBC. In light of the data observed in RIBBON1 and AVADO, and the questions raised on the influence of the chemotherapy partner in driving a specific magnitude of clinical benefit, Genentech believes that there is sufficient rationale for a new trial of Avastin in combination with paclitaxel that would confirm a clinically meaningful difference in PFS similar to that observed in E2100. That is, the available evidence from the full set of first-line MBC trials establishes that the standard for accelerated approval remains met subject to the conduct of a further confirmatory study. There is a reasonable likelihood that the effect for Avastin with paclitaxel is of a magnitude CDER accepts as clinically meaningful.

In considering the import of the Avastin data, in light of the purposes of accelerated approval, it bears noting that Avastin's efficacy data compare favorably to other available treatments for first-line MBC, further supporting accelerated approval. These data for an alternative therapy for first-line MBC provide an instructive reference point and reinforce that the E2100 data represent a meaningful treatment effect for Avastin with paclitaxel. For example, Gemzar—a first-line MBC treatment that CDER referenced as a relevant comparator at the 2007 and 2010 ODAC meetings³²—was approved with a 2.3-month improvement in median time to documented progression of disease (HR 0.65, representing a 35% risk reduction), a smaller

³² Transcript, July 20, 2010 ODAC at 65, 172-74; Transcript, 5 December 2007 ODAC at 34-35, 37, 223.

improvement than that seen in E2100 (5.5-month improvement in median PFS; HR 0.48, representing a 52% risk reduction), and without showing a statistically significant OS improvement.³³

B. Issue 2B: Avastin’s Safety Profile Favors Approval Pending a Confirmatory Study.

The appropriate characterization of Avastin’s safety is a critical component of the evaluation of Avastin’s benefit-risk profile as a treatment option for first-line MBC. On this point, CDER and Genentech agree that Avastin has a well-characterized safety profile, Avastin’s package insert appropriately reflects the extensive experience with the medication in clinical and investigational settings, and the MBC trials do not raise new safety concerns.³⁴ Where Genentech and CDER may diverge is in how they construe Avastin’s known safety profile. CDER has characterized Avastin as presenting greater risks relative to other treatment options for first-line MBC. But the data do not support that assessment.

As with other cytotoxic agents used in the treatment of MBC, Avastin has side effects that are unique to its mechanism of action. However, relative to other therapies used in the treatment of MBC, Avastin presents an acceptable and largely manageable safety profile that supports maintaining accelerated approval.

³³ These data were based on an open-label trial in which the timing and type I error allocation of OS analyses were changed post hoc after the analysis of PFS results. When approved, only interim OS data were available for Gemzar (377 events, representing 86% of the intended information); and those data did not clearly meet the required level of statistical significance ($p > 0.05$ in two sensitivity analyses performed by FDA). Rather, these data suggested a potential OS trend, but that trend dissipated when the prospectively defined final analysis (100% information) became available (HR 0.86; 95% CI 0.71, 1.04) ($p = 0.12$), as indicated in the current product labeling.

³⁴ See Joint Statement, at ¶ 22; FDA, Briefing Book, 20 July 2010 ODAC at 25 (“Overall, the incidence of AEs is not significantly different than currently described in the Avastin package insert.”).

As set forth in more detail above, the pooled data from the first-line MBC trials show fewer overall deaths and fewer deaths due to MBC for Avastin plus chemotherapy versus chemotherapy alone. The incidence of death due to adverse event or protocol therapy was the same for the treatment and control groups—1.8% for each. Hypertension and proteinuria comprised the majority of the increase in Grade 3 or greater adverse events. These side effects are familiar to oncologists and managed per product guidelines, such that they infrequently interfere with treatment delivery. Finally, other serious adverse events that CDER has highlighted are infrequent in absolute terms and also occurred in the chemotherapy-only arms of the Avastin MBC trials (excepting RPLS), albeit at a somewhat lesser frequency. The data thus show that Avastin presents an acceptable oncologic safety profile, and that there are not overriding safety concerns that skew the evaluation of benefit and risk. As the E2100 investigators, leading breast cancer authorities, concluded in their publication on the study: “Most toxic effects were minimal, rarely limited therapy, and did not have a detrimental effect on overall quality of life.”³⁵

CDER agrees that Avastin’s package insert appropriately advises of the spectrum and incidence of Avastin-related safety considerations. MBC patients and their doctors can thus make informed decisions about whether Avastin is an appropriate therapeutic alternative in the face of a life-threatening disease. These treatment decisions necessarily involve an evaluation of Avastin’s risks relative to other MBC therapies, all of which are also associated with serious adverse events. Physicians and patients should be able to determine that, in appropriate clinical

³⁵ Miller et al., *supra* note 9 at 2673.

circumstances, Avastin plus paclitaxel is the optimal therapy available to the patient. For example, Avastin presents a risk profile that is non-overlapping with the risk profile of traditional chemotherapy, which may be beneficial for some patients.

Of course, the benefit-risk profile of Avastin must also be evaluated in the context of the disease setting. As Dr. John Finnie from St. John's Mercy Medical Center has stated, "I would favor maintaining the indication for this targeted therapy for my breast cancer patients, based not only on its safety data but also [on its] consistently seen improved outcomes, on a par with other approved agents in the metastatic setting. . . . The decision by ODAC to consider withdrawing the FDA approval of bevacizumab is based on the lower relative benefit in subsequent studies; however, nearly all medical oncologists could cite examples of patients treated with this agent, showing clinical benefit with very good tolerability."³⁶

III. Issue 3: Approval Should Be Maintained Pending a Further Study.

A. Avastin in MBC Continues to Meet the Standards for Accelerated Approval.

The accelerated approval regulations permit FDA to approve medications for serious and life-threatening diseases like MBC where the available data establish a reasonable likelihood of clinical benefit that can be characterized with further study.³⁷ Correspondingly, withdrawal of accelerated approval should be appropriate only where this standard cannot be satisfied, because there is no reasonable likelihood of clinical benefit and no possibility that additional study might further characterize any existing benefit.

³⁶ Avastin Controversy Shakes Up Oncology Community, *Clinical Oncology News*, October 2010:5:10.

³⁷ See Federal Food, Drug, and Cosmetic Act § 506(b); 21 C.F.R. § 601.41.

In setting forth Issue 3, the Presiding Officer has recognized that withdrawal may not be appropriate even if the statutory and regulatory bases for withdrawal are present. This is consistent with FDA's longstanding acknowledgement that, although the accelerated approval regulations provide for expedited withdrawal, "they do not guarantee that results of studies will be wholly unambiguous or that FDA will always be able to prevail in its view as to the need for withdrawal."³⁸ The facts here justify retaining approval pending a study, particularly because no new safety issue has arisen, the postmarketing studies met their agreed-upon endpoints, and the studies satisfied CDER's standard of showing "demonstrated improvement in progression free survival and evidence that survival is not impaired."³⁹

The only open question is whether the magnitude of benefit observed in the E2100 study is reasonably likely to be confirmed in a second study of Avastin with paclitaxel. Given the meaningful probability that the chemotherapy partner has an impact on the magnitude of benefit, and given that an additional study can resolve this question, accelerated approval should be maintained pending completion of Genentech's further study. It would be contrary to public health to withdraw accelerated approval where the subsequent studies uncovered no new safety risks and continued to show a benefit, albeit at a lower magnitude with different chemotherapy partners. If the confirmatory study fails to meet the standard CDER set at the February 2011 Type B meeting, withdrawal could then appropriately be considered.

Genentech's proposal furthers the principal aim of the accelerated approval program: promoting the availability of innovative treatments for patients with serious, life-

³⁸ 57 Fed. Reg. 58942, 58956 (11 Dec. 1992).

³⁹ Minutes, 26 February 2009 Type B Meeting at 7.

threatening illnesses, subject to further testing. For these patients, ensuring access and choice “can be as important as preventing the marketing of harmful or ineffective products.”⁴⁰

Withdrawal here would fundamentally undermine the goals of the accelerated approval program by prematurely and unnecessarily depriving a vulnerable patient population of a valuable therapy.⁴¹

Maintaining accelerated approval for Avastin with paclitaxel on limited terms subject to a further study is consistent with the regulatory flexibility afforded under the accelerated approval regime. Even where FDA determines that confirmatory trials do not establish clinical benefit, withdrawal is not required and instead should be based on the public health considerations that motivate the accelerated approval statute.⁴² As FDA has previously stated, the agency “must carefully assess each case, and consider the underlying reasons and the consequences of all regulatory options, including their potential impact on patients.”⁴³ FDA may conclude based on that assessment that there is “a subset of patients for whom the drug may nevertheless be effective,” and that “other regulatory tools” are appropriate.⁴⁴

⁴⁰ S. Rep. No. 105-43 at 8 (quoting the Advisory Committee on the Food and Drug Administration chartered by the Secretary of HHS in 1989).

⁴¹ This concern is demonstrated by the limited remaining treatment options for MBC, against which Avastin compares favorably. For example, Avastin compares favorably to Gemzar. The data show a greater PFS benefit from Avastin’s use with paclitaxel—a 5.5-month median PFS improvement with Avastin compared to a 2.3-month improvement in time to progression with Gemzar—and a safety profile for Avastin that is comparable, if not preferred, to the risks associated with Gemzar. Moreover, the Gemzar data do not show an OS benefit.

⁴² See U.S. Government Accountability Office, *New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs on the Basis of Surrogate Endpoints*, GAO-09-866 (September 2009) (“GAO Report”) at 34.

⁴³ GAO Report, App. V, FDA Comments on GAO Report, at 3.

⁴⁴ *Id.* at 3-4.

Genentech's study proposal addresses these points. The new study will further test the evidence indicating that there is a meaningful benefit for Avastin with paclitaxel, and the VEGF-A biomarker element will further the goal of identifying a subgroup of patients who may derive a more substantial benefit from Avastin.

B. Other Expert Bodies and Regulatory Agencies Continue to Support Avastin for MBC.

The actions of other expert bodies and regulatory agencies reinforce the appropriateness of maintaining Avastin's accelerated approval. While FDA should not simply follow the determinations of other expert bodies, the judgments of those bodies speak to the scientific and public health grounds for retaining Avastin as a treatment option pending further study. Following the July 2010 ODAC meeting, the NCCN breast cancer panel unanimously reaffirmed its recommendation of Avastin in combination with paclitaxel, based on the same data reviewed by CDER and the July 2010 ODAC.

The chair of the panel, Dr. Robert Carlson, a medical oncologist at Stanford Comprehensive Cancer Center, noted that "continuing to recommend bevacizumab in metastatic breast cancer shows 'logical consistency' because many approved drugs have also failed to show benefits in survival or quality of life."⁴⁵ As Dr. Carlson explained, the panel discussed bevacizumab three times in the four to five months leading up to the FDA announcement and "was very cognizant that the FDA may withdraw approval."⁴⁶ Upon repeated review, the 27 panel members concluded that there was "no new information in the current data sets that would

⁴⁵ Larkin C. Is the Battle Over Bevacizumab Coverage Looming? *J Natl Compr Canc Netw* 2011;9:261.

⁴⁶ *Id.*

alter the panel's recommendation."⁴⁷ The support of the NCCN's breast cancer panel is notable because of the deep expertise among its membership, which includes clinicians and researchers with specific breast cancer experience and affiliations with major cancer centers across the United States.⁴⁸

Also based on the same clinical data reviewed by CDER, the EMA's CHMP confirmed its view that "the benefits of Avastin in combination with paclitaxel outweigh its risks," and that "this combination remains a valuable treatment option for patients suffering from metastatic breast cancer."⁴⁹ The European Commission, the executive body of the European Union, later adopted the EMA's position. The European regulators reached these judgments after deciding, based on submission of the RIBBON1 data, to conduct a full reassessment of the previously approved uses of Avastin with paclitaxel and docetaxel, retaining approval of use with paclitaxel but not docetaxel. The CHMP also recently adopted a positive opinion on the use of Avastin in combination with capecitabine based on further consideration of the RIBBON1 study, determining that this combination represents a meaningful treatment option for patients.⁵⁰

It would be misguided to dismiss the EMA's actions based on the type of approval granted in Europe (equivalent to full approval in the United States) and differences in

⁴⁷ *Id.*

⁴⁸ In contrast, the July 2010 ODAC was more heterogeneous, with a minority of its members specializing in breast oncology or women's cancers.

⁴⁹ Press Release, European Medicines Agency, European Medicines Agency Completes Its review of Avastin Used in Breast Cancer (16 Dec. 2010), *available at* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/12/news_detail_001166.jsp&mu rl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jscenabled=true (last visited 12 May 2011).

⁵⁰ *See supra* note 23.

the European regulatory scheme. Like the United States approval framework, the European framework is focused on an assessment of benefit and risk, as well as reaching approval decisions that are appropriate for patients and physicians based on the science and public health. EMA's decision and the decisions of various other health authorities around the world⁵¹ reflect consistent expert views that the science supports retaining Avastin with paclitaxel.

The decisions of the NCCN, EMA, and other health authorities correspond with the views of many treating oncologists, who have adopted Avastin as a standard of care in first-line MBC and who continue to believe in the value of this treatment. This collective body of expert opinion further supports retaining approval pending further study. The very fact that these expert bodies have come to directly the opposite conclusions as CDER further reinforces the value of the middle-ground approach of retaining physician and patient choice pending completion of a further study.

C. CDER's New Approval Standard May Deter Development of New Treatments for First-Line MBC.

CDER's withdrawal decision rests upon a new approval standard. That standard has not been established through written public guidance on hazard ratios or median PFS relative to control. However, the proposal for Avastin's withdrawal suggests that either a substantial PFS improvement (replicating or exceeding the results of the E2100 study) or an OS benefit is necessary for approval. The agency has not clearly and consistently articulated, or applied, this new standard, creating an unpredictable regulatory setting and risking confusion among

⁵¹ Since the July 2010 ODAC, in addition to the European Union, six countries have affirmed Avastin's MBC indication with paclitaxel: Australia, Brazil, South Korea, Russia, Singapore, and Mexico. Avastin is currently approved in combination with paclitaxel for MBC in 84 countries. No country has withdrawn approval for Avastin's MBC indication with paclitaxel.

oncologic product sponsors that may deter future development in MBC. This lack of predictability and consistency raises special concern in an area of high unmet medical need.

1. An OS benefit is increasingly difficult to show in first-line MBC studies.

Like CDER, Genentech recognizes the importance of survival as a measure of clinical benefit. At the same time, no treatment for first-line MBC has been approved in recent years based on a clear OS benefit. To demand that first-line MBC treatments demonstrate an OS benefit (if they cannot show a large PFS effect) underestimates the difficulties of conducting a study that will show an OS benefit. Reliably demonstrating an OS effect is especially difficult in first-line MBC, where the period of survival after initial progression is typically long relative to time receiving first-line treatment. A study powered to identify a survival improvement could require a lengthy accrual period, thousands of participants, and several years to generate data, factors that risk making such a study infeasible to conduct.⁵²

In contrast, FDA has recognized PFS as an appropriate endpoint for approval in cancer trials.⁵³ PFS permits the evaluation of tumor control with reasonable sample sizes and follow-up times and is unlikely to be confounded by subsequent lines of therapy. And PFS can be independently confirmed to account for potential systematic bias in its measurement.⁵⁴

Prolonged PFS also is a meaningful benefit for many patients, because it delays the introduction

⁵² Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. *J Natl Cancer Inst* 2009; 101: 1642-9.

⁵³ U.S. Food & Drug Administration, Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007) at 9.

⁵⁴ See Amit O, Bushnell W, Dodd L, Roach N, Sargent D. Blinded independent central review of the progression-free survival endpoint. *The Oncologist*. 2010; 15: 492-495.

of new therapies, a transition that can have significant psychological consequences, due to the attendant uncertainties, and cause additional side effects.

In the past 20 years, treatments approved on the basis of typically modest effects on disease progression endpoints, like PFS, have collectively contributed to an incremental increase in survival.⁵⁵ An approval standard that mandates an OS benefit in first-line MBC might prevent access to therapies that could contribute to the steady OS gains in MBC.

2. CDER is not applying a clear, consistent standard.

CDER has not been clear in articulating a consistent standard for the showing of clinical benefit necessary to support approval for treatments in first-line MBC. This is seen in the regulatory history for Avastin in MBC. The uncertainty resulting from the lack of a clear, predictable, and consistent regulatory standard risks discouraging oncologic drug development in MBC.

When CDER granted accelerated approval to Avastin for first-line MBC, the agency accepted AVADO and RIBBON1 as confirmatory studies, with PFS as the primary endpoint. CDER did not establish a specific magnitude of PFS improvement necessary for continued approval and, in fact, accepted AVADO as a confirmatory study aware that the final protocol-defined PFS data showed an improvement in median PFS at the time of 0.8 months with an HR of 0.64.⁵⁶ Similarly, the agency knew that neither confirmatory study was powered to

⁵⁵ Giordano SH, Buzdar AU, Smith TL, et al. Is breast cancer survival improving? Trends in survival for patients with recurrent breast cancer diagnosed from 1974 through 2000. *Cancer* 2004;100:44–52. *See also* Chia SK, Speers CH, D'yachkova Y, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 2007;110:973–9.

⁵⁶ The interim OS data for AVADO showed a hazard ratio of 0.65, or a 35% risk reduction.

show an OS benefit.⁵⁷ CDER accordingly premised conversion from accelerated to full approval on a “demonstrated improvement in progression-free survival and evidence that survival is not impaired.”⁵⁸

Although it was clear that AVADO and RIBBON1 were not powered to show an OS benefit, the agency now cites the studies for failing to show a statistically significant OS effect. Then, CDER stated only after its decision to withdraw Avastin’s MBC indication that any PFS effect “must confirm the magnitude of treatment effect of E2100.”⁵⁹ Significantly, CDER has not provided general guidance to the broader industry on these issues, limiting its actions to Avastin. CDER also has not articulated a clear rationale for its view that a 5.5-month improvement in median PFS is clinically meaningful but lesser improvements are not.

It is important to maintain clear and consistent approval criteria to establish a predictable regulatory environment that minimizes uncertainty and facilitates development efforts by sponsors. Patient advocates and members of the oncology development community have expressed this concern. The Melanoma Research Foundation, for example, noted the increased “regulatory burden on drug development” caused by poorly-defined approval standards: “[C]riteria that are unclear or are changed mid-process adds to cost of development and, more significantly, results in delays in ensuring patients have access to drugs that may be life-saving.”⁶⁰ Other groups have also urged FDA to provide “standards and consistent

⁵⁷ See Minutes, 26 February 2009 Type B Meeting at 3.

⁵⁸ *Id.* at 7.

⁵⁹ Minutes, 22 February 2011 Type B Meeting at 3.

⁶⁰ Comment, Melanoma Research Foundation, No. FDA-2010-N-0621-0022 (14 January 2011).

processes” for approval.⁶¹ CDER should not take adverse regulatory action that would deprive thousands of MBC patients of a valuable treatment, having failed to set out clear standards for drug development *ex ante*.

3. The agency should exercise flexibility in its application of the accelerated approval standard.

The challenges of defining and proving benefit in the first-line MBC setting caution against adoption of an overly rigid regulatory approach. As discussed, the Presiding Officer has recognized the flexibility the FDA has in determining whether to withdraw accelerated approval. That is, while the statute and regulations *allow* withdrawal when a confirmatory trial fails to verify clinical benefit, they do not *require* withdrawal under these circumstances. The exercise of that discretion is particularly appropriate on these facts. Withdrawal would be appropriate if a serious new safety signal were identified; none has been identified here. Withdrawal might also be appropriate if no benefit were seen in the confirmatory trials; a statistically significant benefit was observed here.

The only basis for withdrawal on these facts is the concern that the benefit seen in the confirmatory trials was smaller (balanced against the risks) than in the trial that supported

⁶¹ Comment, Research Advocacy Network, No. FDA-2010-N-0621-0043 (18 January 2011); *see also* Comment, Marti Nelson Cancer Foundation, No. FDA-2010-N-0621-0111 (14 February 2011) (arguing that the need to “further consider, and more objectively define, clinical significance versus statistical significance in the context of the use of progression free survival versus overall survival as clinical trial endpoints to support drug approval applications” is an issue of “broad public health and public policy importance” and that “a public hearing on the immediate bevacizumab issue may contribute important understanding” on the issue); Comment, Men’s Health Network, No. FDA-2010-N-0621-0027 (19 January 2011) (noting that “we should avoid action which would stifle medical research and innovation” and that FDA’s decision on Avastin “may set a bad precedent moving forward”); Comment, Colon Cancer Alliance, No. FDA-2010-N-0621-0049 (7 February 2011) (“[W]e are concerned about the FDA processes in place and what we perceive as [a] lack of consistent standards.”); Comment, Ovarian Cancer National Alliance, No. FDA-2010-N-0621-0003 (16 December 2010) (“[T]he FDA decision calls into question the use of Progression Free Survival (PFS) as an endpoint for cancer clinical trials. Previously, the FDA has approved treatments when they have been shown to increase PFS.”).

accelerated approval. This should not be a ground for an inflexible application of the withdrawal standard when there is an alternate explanation for the lesser effect that is consistent with CDER's prior views—the choice of chemotherapy partner matters—and where that explanation will be elucidated through a further trial focused on this precise question.

These facts justify the exercise of the regulatory flexibility that the Presiding Officer has recognized. That regulatory flexibility is intended for cases like this, where a formulaic application of the withdrawal standard would deprive patients and physicians of the choice intended by the accelerated approval program—and do so in the face of continued findings of benefit, a well-understood safety profile, and a viable option for providing a clearer answer to the remaining scientific questions.

* * *

For these reasons, Genentech requests that FDA maintain Avastin's accelerated approval in combination with paclitaxel subject to a confirmatory study intended to characterize further the clinical benefit of this therapeutic pairing in first-line MBC.

Respectfully submitted,

Sandra J. Horning, M.D.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Michael S. Labson
Paul W. Schmidt
COVINGTON & BURLING LLP
1201 Pennsylvania Ave., NW
Washington, DC 20004-2401

Counsel for Genentech, Inc.

May 13, 2011