Post-Hearing Submission 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

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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.

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EXECUTIVE SUMMARY

There remains indisputable need for additional treatments for metastatic breast cancer (MBC), as was starkly demonstrated at the hearing on the proposal of the Center for Drug Evaluation and Research (CDER) to withdraw the breast cancer indication for Avastin. The public testimony, data, and legal arguments demonstrate why, in light of this need, Avastin in combination with paclitaxel should retain its accelerated approval.

Retaining accelerated approval will allow Avastin to remain available to the patients who have the greatest unmet need, while Genentech addresses CDER's views regarding Avastin in MBC by: (1) conducting a confirmatory trial of Avastin with weekly paclitaxel; (2) adopting labeling to direct doctors to the most appropriate MBC cases; and (3) undertaking further physician and patient communications to emphasize the efficacy and safety data, thus supporting informed decision making regarding Avastin.

The data and testimony presented at the hearing established the following core points supporting Genentech's proposal.

1. There Are Significant Unmet Medical Needs in First-Line Metastatic Breast Cancer. Accelerated approval exists to facilitate the availability of additional treatment options in areas of unmet medical need. In first-line HER2-negative MBC, the need for greater treatments is profound. This is even more true for patients with aggressive disease where few other therapies are considered appropriate, including patients with triple-negative MBC (HER2-negative and hormone receptor (HR)-negative disease, or TNBC) and HER2-negative, hormone receptor-positive disease with characteristics such as visceral metastases, high tumor burden, and rapid disease progression. The accelerated approval provisions require that this need for additional treatment options guide FDA's consideration of Avastin.

2. Avastin in Combination with Weekly Paclitaxel Confers a Clinically Meaningful Benefit in First-Line MBC. Avastin plus weekly paclitaxel, based on the E2100 study, met CDER's standard for accelerated approval by demonstrating a clinically meaningful benefit over existing therapies and addressing an unmet medical need. CDER reiterated at the hearing that it accepts progression-free survival (PFS) as a clinically meaningful endpoint for first-line MBC treatments, even in the absence of a proven survival or quality of life benefit. In the E2100 study, the effect for Avastin with paclitaxel was substantial – Avastin provided an advantage over paclitaxel alone by reducing the risk of disease progression or death by 52% and increasing median PFS by 5.5 months. CDER agrees that this magnitude of PFS benefit is meaningful and will support full approval if replicated in a new study of Avastin with paclitaxel.

Just as CDER found in 2008, the E2100 data are reliable today and compare favorably to the data supporting other available treatments. In granting accelerated approval in 2008, CDER carefully reviewed the design and conduct of E2100 study, expressing confidence about the points it now cites as concerns. No other medication has been approved for first-line MBC since that time, and the data on Avastin with paclitaxel compare favorably to the data that support the approval of Gemzar, the only other treatment indicated for first-line treatment that encompasses HER2-negative MBC.

The greatest benefit from Avastin was seen in combination with weekly paclitaxel in study E2100; a lesser magnitude of effect, particularly on median PFS, was observed with other chemotherapy partners. The most plausible interpretation of these data, including in light of the greater total exposure with weekly paclitaxel, is that Avastin with weekly paclitaxel provides a greater magnitude of benefit than Avastin with other chemotherapy partners. This interpretation of the data is bolstered by prior statements from CDER and by the ongoing

recognition from other scientific bodies – including the European Medicines Agency (EMA), over 80 other regulators around the world, and the National Comprehensive Cancer Network (NCCN) – that Avastin's effect varies by chemotherapy partner. This interpretation calls for retaining accelerated approval with paclitaxel alone, subject to a confirmatory trial examining Avastin with weekly paclitaxel.

3. Avastin's Well-Understood and Unchanged Safety Profile Supports Maintaining Accelerated Approval. The hearing made clear that there are no new safety findings on Avastin. CDER did not contest the fact that there were fewer total deaths on Avastin than with chemotherapy alone and no difference in treatment-related deaths. The most common adverse events – proteinuria and hypertension – can be medically managed, are unlikely to lead to treatment discontinuation, and (as emerging data demonstrate) are generally reversible after discontinuation. Nor did CDER refute Genentech's showing that Avastin's risks are in line with those of other MBC treatments, particularly combination chemotherapy regimens that are deemed necessary to achieve tumor control for patients with aggressive disease characteristics. The record on safety thus shows that there are not new or overriding concerns, further supporting maintaining Avastin's approval.

4. The Accelerated Approval Statute and the Scientific Data Support Genentech's Middle-Ground Proposal. Withdrawal of access to Avastin for all patients would fundamentally undermine the goals of accelerated approval by prematurely and unnecessarily depriving patients and physicians of a treatment choice where the safety profile is unchanged and well-understood, the confirmatory trials were positive, and a viable study could more definitively confirm clinical benefit.

In response to CDER's contrary views, Genentech has set forth a middle-ground proposal to maintain accelerated approval, which is motivated by the primary goals of preserving access to Avastin for appropriate MBC patients, addressing the significant unmet medical need in first-line MBC, and bolstering the data set supporting Avastin in combination with paclitaxel. This proposal would allow continued use of Avastin with paclitaxel only, with limitations such as labeling directed toward those patients with aggressive disease and the fewest treatment options, while Genentech conducts a confirmatory trial aimed squarely at the required showing CDER has now articulated.

The patients this proposal addresses – particularly patients with aggressive disease characteristics such as visceral metastases, high tumor burden, and rapid disease progression – present the greatest unmet medical need. As Dr. Joyce O'Shaughnessy, Co-Chair of Breast Cancer Research at Baylor-Sammons Cancer Center, noted at the hearing: "We would be doing a very great disservice to women to take this away from them while this confirmatory trial is being conducted."[1]

The facts here particularly support the exercise of CDER's discretion to retain approval. Genentech did not previously design a trial to replicate Avastin's magnitude of effect with paclitaxel because it reasonably understood – from proactively sharing data with CDER as early as 2008 (prior to accelerated approval) showing a lesser magnitude of effect with other chemotherapy partners – that CDER instead sought a consistent showing of improved PFS, which Genentech demonstrated. The unforeseen circumstances of this misunderstanding, and the science indicating that the chemotherapy partner affects the magnitude of PFS benefit,

[1] Transcript, June 29, 2011 Public Hearing at 181:19-21.

provide further support for retaining approval with paclitaxel subject to a confirmatory trial designed to meet the standards CDER has now articulated. The agency has appropriately exercised regulatory flexibility in the past when initial postmarketing trials have not confirmed clinical benefit, and it has never previously sought to withdraw accelerated approval where well-controlled confirmatory trials agreed upon with CDER were conducted expeditiously and showed positive results. In light of the medical need here, Avastin should not be the case where the agency departs from its established practices.

The scientific basis for Genentech's proposed approach is demonstrated by the predominant view of other regulators and the NCCN, who endorse the use of Avastin with paclitaxel. These views weigh heavily against the negative vote of the Oncologic Drugs Advisory Committee (ODAC), which did not bring to bear the same breast cancer expertise as an organization like NCCN, and which premised its negative vote on a disagreement with even CDER as to whether PFS may establish benefit in first-line MBC. The considerable body of scientific determinations supporting Avastin with paclitaxel – acknowledged by CDER to be reasonable contrary views – and the ability to address CDER's questions through other measures consistent with the accelerated approval process, underscore why the Commissioner can and should retain Avastin's accelerated approval under the approach offered by Genentech.

BACKGROUND

The hearing highlighted the regulatory history of Avastin in MBC and the core facts on which CDER and Genentech agree. This history and these facts are summarized below and form the basis for Genentech's proposal to retain accelerated approval.

A. CDER's Approval of Avastin for MBC

CDER granted accelerated approval for Avastin in MBC by determining that Avastin provides a meaningful therapeutic benefit over existing treatments in the first-line

treatment of HER2-negative disease. CDER's approval was based on the E2100 study, which demonstrated that Avastin paired with weekly paclitaxel significantly reduces the risk of disease progression or death by 52% (HR 0.48, $p<0.0001$), and increases the median time before death or tumor progression (median PFS) by 5.5 months. No other treatment for first-line HER2-negative MBC prior to or after the E2100 study has shown a comparable benefit.

CDER limited its approval to Avastin with a single chemotherapy partner, paclitaxel, for two reasons: E2100 examined only Avastin with paclitaxel, and CDER had results from another study – AVF2119g – that did not show a PFS benefit from Avastin with capecitabine in later-line treatment settings.

CDER then conditioned full approval on positive results from two first-line studies: AVADO (Avastin with docetaxel) and RIBBON1 (Avastin with either a taxane/anthracycline or capecitabine regimen). CDER was aware that these studies were not designed to replicate the 5.5-month median PFS difference seen in E2100,[2] and prior to approving Avastin for MBC, CDER had *final* AVADO PFS data showing a median PFS improvement of 0.8 months.[3] In 2008, CDER specifically cited these AVADO data as supporting accelerated approval.[4]

Based on these facts, Genentech understood that the PFS results from AVADO, along with a positive PFS showing from RIBBON1, would support full approval. Thus,

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[2] Both studies targeted hazard ratios (0.7-0.75) expected to translate into median PFS differences of 2-3 months.

[3] The difference in median PFS (0.8 months) that was provided in the slide deck to CDER prior to accelerated approval used the definition of non-protocol therapy pre-specified for the European submission. The difference in median PFS (0.9 months) provided in the final study report submitted to CDER used a slightly different definition of non-protocol therapy that was pre-specified in the US statistical analysis protocol and reviewed by CDER.

[4] Office of Oncology Drug Products, Office Director's Memorandum re BL STN 125085/91, Feb. 21, 2008 [hereinafter "Office Director's Memo"] at 3; *see also* "PFS is a Benefit 'In the Right Context,' Pazdur Says in Q&A on Avastin Approval," The Cancer Letter, Feb. 29, 2008 at 2.

Genentech did not design an additional confirmatory trial intended to replicate the same magnitude of PFS seen with paclitaxel in E2100.

In February 2009, Genentech met with CDER for a pre-sBLA meeting. Before the meeting, Genentech provided CDER with the top-line *final* PFS data from both confirmatory trials, showing median PFS improvements of 0.9 months (AVADO), 1.2 months (RIBBON1 taxane/anthracycline), and 2.9 months (RIBBON1 capecitabine). CDER did not inform Genentech during or after this meeting that a greater magnitude of PFS would be required; instead, CDER informed Genentech that full approval would follow from "demonstrated improvement in progression-free survival and evidence that survival is not impaired."[5]

The AVADO and RIBBON1 studies met this standard, as articulated at the pre-sBLA meeting. The studies collectively showed that "survival is not impaired," and each demonstrated "improvement in progression-free survival."[6]

Genentech accordingly sought full approval, with a broader range of chemotherapy partners. The July 2010 ODAC, however, voted against expanding Avastin's indication and, to Genentech's surprise, voted to withdraw accelerated approval. Genentech responded in August 2010 by proposing a confirmatory trial of Avastin with paclitaxel, with a biomarker component, intended to replicate the magnitude of median PFS seen in E2100. CDER has since confirmed that such a study would support full approval; however, CDER continues to seek withdrawal of the MBC indication.

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[5] Type B Meeting Minutes, Feb. 26, 2009 at 7.

[6] AVADO showed a 38% risk reduction (HR 0.62, 95% CI 0.48, 0.79) (p=0.0003); the RIBBON1 taxane/anthracycline arm showed a 36% risk reduction (HR 0.64, 95% CI 0.52, 0.80) (p<0.0001); and the RIBBON1 capecitabine arm showed a 31% risk reduction (HR 0.69, 95% CI 0.56, 0.84) (p=0.0002).

B. The June 28-29, 2011 Hearing

On June 28 and 29, 2011, Presiding Officer Dr. Karen Midthun oversaw the hearing in this matter, receiving statements from CDER, Genentech, and 34 public presenters. The public presenters echoed the public docket in overwhelmingly supporting Avastin for MBC.[7]

The hearing established key facts regarding Avastin's efficacy and safety, CDER's discretion to retain approval, and the details of Genentech's confirmatory study.

1. *Avastin's Efficacy in MBC:* CDER and Genentech agreed at the hearing that the magnitude of PFS benefit observed in E2100 constitutes clinical benefit and supports approval, even without a showing of improvement in overall survival or quality of life.[8] That position, CDER confirmed, reflects FDA's broader acceptance of PFS as an endpoint that can support oncology approvals.[9]

CDER and Genentech also agreed that the E2100 data show an effect from Avastin on MBC: "nobody is arguing whether an effect occurs. The robustness was never an issue."[10] The parties disagree over whether the magnitude of the effect may vary by chemotherapy partner, although CDER acknowledged its pre-hearing recognition that "the

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[7] Thirty of the 34 presenters – including patients, oncologists, and advocacy group representatives – testified in favor of retaining approval. All but four of the more than 400 written docket statements, including one comment attaching a petition with over 11,000 signatures, also support retaining approval. Comment, Christi Turnage, Docket No. FDA-2010-N-0621-0271; Transcript, June 28, 2011 Public Hearing at 99:7-14.

[8] Transcript, June 28, 2011 Public Hearing at 214:18-215:5.

[9] *Id.* at 215:18-216:4 ("MR. SCHMIDT: . . . [D]oes CDER stand behind those statements that progression-free survival can be an approvable endpoint and that overall survival is not always required? DR. PAZDUR: Yes, we do . . . .").

[10] Transcript, June 28, 2011 Public Hearing at 306:19-21; *see also id.* at 231:22-232:3 ("[T]here is a treatment effect here. The robustness issue is not in debate, in our mind").

treatment effect will vary according to the chemotherapy regimen used."[11] The parties also disagree over whether the E2100 results were reliable, a concern CDER conceded that it had carefully vetted pre-approval.[12]

2. *Avastin's Safety Profile:* CDER and Genentech agreed at the hearing that Avastin's safety profile has not changed since the medication's approval for first-line MBC, and that the safety profile is fairly described in the Avastin labeling.[13] Genentech presented data at the hearing that respond to the core safety concerns that CDER has raised, including showing that there were fewer total and MBC deaths, and an identical rate (1.8%) of treatment-related deaths, in the pooled Avastin standard-dose arms compared to the chemotherapy-only arms.[14]

Ultimately, CDER conceded that its withdrawal proposal is not driven by a shift in Avastin's safety profile, which is well-characterized, generally manageable, and known to oncologists.[15] Rather, it is the result of the parties' differing views on Avastin's clinical benefit relative to those risks.

3. *CDER's Discretion and Genentech's Proposal:* CDER acknowledged that FDA has legal discretion to maintain accelerated approval here.[16] At the hearing, Genentech expanded

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[11] Type B Meeting Minutes, Jan. 10, 2006 at 2.

[12] Transcript, June 28, 2011 Public Hearing at 228:17-229:6; *see also* Office Director's Memo at 4 (noting that "[b]ecause of the close agreement between the two assessments [ ], systemic bias seems unlikely"); *id.* ("Pre-specified sensitivity analyses corroborate the maintenance of a treatment effect in handling missing data."). As discussed further below, Genentech carefully addressed these concerns during the hearing. Transcript, June 29, 2011 Public Hearing at 52:6-62:14.

[13] Transcript, June 28, 2011 Public Hearing at 213:17-214:2.

[14] Transcript, June 29, 2011 Public Hearing at 24:21-25:6; Genentech Presentation Slides, June 29, 2011 Public Hearing at 18.

[15] Transcript, June 28, 2011 Public Hearing at 214:17-215:11.

[16] *Id.* at 262:15-263:4.

on its proposal for FDA to exercise that discretion by retaining access while Genentech addresses the concerns CDER has raised. Specifically, Genentech:

- Provided details on its confirmatory study of Avastin with paclitaxel;
- Proposed directing use toward the forms of MBC with the greatest medical need (with proposed labeling to implement this approach included in Appendix A); and
- Described additional safety and efficacy communications it could undertake to address CDER's concerns (with a proposed Risk Evaluation and Mitigation Strategy [REMS] and MedGuide included in Appendix B).

In the face of Genentech's proposal, which is motivated by its conviction that Avastin should be available for appropriate MBC patients, CDER admitted that it has considered no alternatives other than withdrawal.[17]

ARGUMENT

The hearing testimony established the unmet medical need for effective MBC treatments, particularly for patients with aggressive disease. At the same time, the testimony underscored the agreement between CDER and Genentech on core facts: Avastin has an effect on MBC in every first-line study, its safety profile is well-understood, and CDER possesses discretion, which should be guided by the degree of unmet medical need, to retain Avastin's approval. On these facts, where the debate lies over the *magnitude* of benefit and whether that magnitude varies by chemotherapy partner, public health goals counsel that Avastin be retained as an approved choice, subject to further study, particularly for the patients with disease characteristics for which other therapies are less appropriate.

[17] Transcript, June 28, 2011 Public Hearing at 268:17-22.

I. There Are Significant Unmet Medical Needs in First-Line Metastatic Breast Cancer.

The guiding purpose of accelerated approval is to increase access to therapies that "demonstrate[] the potential to address unmet medical needs for [a serious or life-threatening] condition."[18] As Congress stated in creating accelerated approval, approving promising new therapies that address unmet medical need "can be as important as preventing the marketing of harmful or ineffective products . . . especially [] for people with life-threatening illnesses and for diseases for which alternative therapies have not been approved."[19]

MBC represents the type of unmet medical need for which accelerated approval was created. In 2010, approximately 40,000 women in the United States died of this incurable condition. There are limited treatment options for MBC, even though it demands a range of meaningful options. The need for additional treatment options in first-line MBC is particularly profound for patients with characteristics of aggressive disease, which are most prevalent in TNBC but also seen in HR-positive HER2-negative disease – for example, visceral metastases, high tumor burden, rapid disease progression – where few other therapies are considered appropriate. As Dr. Joyce O'Shaughnessy explained at the hearing: "Loss of access to Avastin-paclitaxel would most acutely impact metastatic triple negative patients who have few effective treatment options, as well as patients with aggressive symptomatic ER-positive breast cancer."[20]

Dr. Stanley Waintraub, Co-Chief of the John Theurer Cancer Center Breast Oncology Division, echoed this same point: "Avastin coming off the market would be

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[18] Federal Food, Drug, and Cosmetic Act (FDCA) § 506(a)(1), 21 U.S.C. § 356(a)(1).

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

[20] Transcript, June 29, 2011 Public Hearing at 86:8-12.

devastating to my breast cancer patients, especially the triple negative group."[21] The Triple Negative Breast Cancer Foundation, in a comment to the public docket, further spoke to the impact on TNBC patients from withdrawal: "This is not a population that deserves the hardships that will come from removal of what may be, for some women, their last hope for life."[22]

At the hearing CDER espoused a fundamentally different view – namely, that there are multiple treatment options for first-line MBC:

> This issue of an unmet medical need I feel really needs to be addressed, also. When we use that term in a regulatory context, what we're generally referring to is no available therapy. And I don't think anybody here at this time would say first-line metastatic breast cancer has no available therapy. And by available therapy, I'm talking about not only approved drugs, but drugs that are used commonly by physicians, such as CAF, you name it, Taxotere, Taxol, you name it, those drugs are available for a first-line therapy.[23]

This view contradicted CDER's own pre-hearing view, expressed in the parties' Joint Statement of Undisputed Facts, that "[t]here is unmet medical need for additional safe and effective therapies for MBC."[24] Similarly, CDER acknowledged in December 2010, upon issuing the NOOH, that "there are not enough effective treatments for this cancer."[25]

CDER's prior recognition of the need for additional treatment options in first-line MBC is consistent with FDA's established policies on medical need. FDA Guidance defines an unmet medical need as a "medical need that is *not addressed adequately by an existing*

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[21] Transcript, June 28, 2011 Public Hearing at 50:4-11.

[22] Comment, Triple Negative Breast Cancer Foundation, Docket No. FDA-2010-N-0621-0464 (July 26, 2011).

[23] Transcript, June 28, 2011 Public Hearing at 282:5-16 (statement of Dr. Pazdur).

[24] Joint Statement of Undisputed Facts and Select Issues in Dispute of the FDA Center for Drug Evaluation and Research and Genentech, Inc. (Apr. 7, 2011) [hereinafter "Joint Statement"] at 2.

[25] Letter from Dr. Janet Woodcock to Breast Cancer Community, Dec. 16, 2010, *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237286.pdf.

therapy."[26] This standard may be met when there are *no* alternate therapies or, as here, when a new therapy may benefit patients who are unable to tolerate or are unresponsive to alternative therapies.[27] Also, available therapy is generally interpreted as *approved* therapy.[28] The views that CDER expressed at the hearing – that unmet medical need refers only to no available therapy,[29] and that available therapies for first-line MBC include unapproved treatments[30] – cannot be reconciled with these prior statements.

Two CDER slides from the hearing demonstrate precisely why there remains an acute need for additional MBC treatments.[31] These slides show that FDA has approved only one non-hormonal therapy – Gemzar – in the past 30 years covering HER2-negative MBC.[32] And Gemzar's data show limited efficacy and meaningful risks, reinforcing the unmet medical need.

The accelerated approval process requires that this need guide FDA's consideration of Avastin. The accelerated approval statute embodies Congress's intent that the agency accept uncertainty where there is potential benefit and significant unmet need. Thus, CDER's disagreement with patients and specialists in the MBC community over the unmet

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[26] FDA, Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review (2006) at 6 (emphasis added).

[27] *Id.*

[28] FDA, Guidance for Industry: Available Therapy (2004) at 5; *see also id.* at 4 ("products that are used off-label for the indication at issue and products that have not had formal FDA review are rarely considered available therapy").

[29] Transcript, June 28, 2011 Public Hearing at 282:8-16.

[30] *Id.* at 282:5-16.

[31] CDER Presentation Backup Slides, June 28, 2011 Public Hearing at 99 and 100.

[32] CDER Presentation Backup Slides, June 28, 2011 Public Hearing at 99; *see also* Transcript, June 28, 2011 Public Hearing at 309:16-310:5. The pre-1962 treatments on CDER's slides were approved under a different efficacy standard than presently exists and have been acknowledged as insufficient to address the need for effective MBC treatments. The other non-hormonal agents that CDER described at the hearing are approved only for HER2-positive disease or 2nd- and 3rd-line MBC, and all but one of those are not approved for combination use, the most relevant alternative to Avastin.

medical need in first-line MBC generally – and particularly in aggressive forms of MBC such as TNBC – is one of the central issues before the Commissioner.

If there truly is profound unmet need, as CDER previously has recognized, then CDER's overly skeptical interpretation of the Avastin data is improper. Moreover, this need for additional treatments highlights the inappropriate rigidity reflected in CDER's admission that there is no "proposal [other than withdrawal] . . . that CDER has considered for keeping this medicine available for metastatic breast cancer patients."[33]

II. Avastin in Combination with Weekly Paclitaxel Confers a Clinically Meaningful Benefit in First-Line MBC.

When granting accelerated approval in 2008, CDER determined that "[t]he addition of Avastin to paclitaxel is an improvement over available therapy (single-agent paclitaxel) in a serious or life-threatening disease (metastatic breast cancer)."[34] This determination remains true today.

A. The Data Show Benefit for Avastin with Paclitaxel.

The data from E2100 continue to show a striking benefit in first-line MBC for Avastin with weekly paclitaxel relative to other therapies, including in light of the current dataset. CDER at the hearing stated that it accepts PFS as a clinically meaningful endpoint for first-line MBC treatments in the absence of a proven survival or quality of life benefit.[35] CDER also still accepts that the 52% risk reduction and 5.5-month improvement in median PFS shown

[33] Transcript, June 28, 2011 Public Hearing at 268:17-22.

[34] Office Director's Memo, at 5.

[35] Transcript, June 28, 2011 Public Hearing at 215:18-22.

in E2100 are clinically meaningful, and it stated that replication of these results in a new study would support *full* approval.[36]

No new medications have been approved for first-line MBC since FDA's approval of Avastin, and the Avastin data continue to compare favorably to the data for Gemzar, the only other medication from the last three decades with a first-line approval that includes HER2-negative MBC. While E2100 showed a 5.5-month median PFS improvement with Avastin, with a hazard ratio of 0.48, Gemzar showed a lesser magnitude of benefit more in line with the other first-line Avastin studies: a 2.3-month improvement in median time to documented disease progression, with a hazard ratio of 0.65.[37] Moreover, the degree of risk associated with Gemzar is considerable.[38]

The EMA, numerous other global health authorities (including Australia, Brazil, Mexico, and South Korea), and the NCCN have each considered the entire current data set for Avastin, with each specifically concluding that Avastin in combination with paclitaxel is a valuable treatment in first-line MBC. The NCCN reaffirmed this view in October 2010 and again, following the Avastin hearing, in July 2011. The EMA's Committee for Medicinal Products for Human Use (CHMP) found that "Avastin has been *convincingly shown* to prolong

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[36] Joint Statement, at ¶ 16.

[37] Gemzar's 2.3-month median time to documented disease progression improvement compares to median PFS improvements of 2.9 months in the RIBBON1 capecitabine arm, 1.2 months in the RIBBON1 taxane/anthracycline arm, and 0.9 months in AVADO. Gemzar's hazard ratio of 0.65 compares with hazard ratios of 0.62 in AVADO, 0.64 in the RIBBON1 taxane/anthracycline arm, and 0.69 in the RIBBON1 capecitabine arm.

With respect to OS, when approved only interim OS data were available for Gemzar (377 events, representing 86% of the intended information). The CDER review indicated that the data did not clearly meet the required level of statistical significance ($p>0.05$ in two sensitivity analyses performed by CDER); rather, the CDER reviewer indicated that these data suggested an OS trend. That trend dissipated when the 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.

[38] The non-overlapping toxicities of Avastin relative to those of its chemotherapy partners – a function of Avastin's mechanism of action as an anti-angiogenic biologic – may allow some patients to tolerate combination therapy where Gemzar plus paclitaxel or other chemotherapy combinations would present unacceptable toxicities.

progression-free survival without a negative effect on overall survival, *and the new study data [AVADO and RIBBON1] support this conclusion*."[39]

CDER's view is at the other extreme. CDER accepts that AVADO and RIBBON1 show that Avastin is effective in first-line MBC with chemotherapies other than paclitaxel. CDER acted on this view in approving Avastin in 2008, requesting an early look at the definitive AVADO PFS data before approving Avastin for MBC in 2008 to confirm AVADO was a "positive study" so that CDER would not "go out on a limb" with the approval.[40] CDER nonetheless now seeks withdrawal by reversing its prior acceptance of E2100, rejecting the potential for genuine differences across various chemotherapies, and focusing on the least favorable aspects of the PFS data (medians rather than hazard ratios) in AVADO and RIBBON1.

This interpretation of the data is unduly restrictive. The efficacy data for Avastin with paclitaxel have been reinforced and not negated by the study results testing Avastin in combination with other chemotherapies, and the unmet medical need for first-line MBC persists.

B. The Data from E2100 are a Reliable Measure of the Efficacy of Avastin in Combination with Weekly Paclitaxel.

CDER's attack on the reliability of the E2100 results is contrary to its own prior acceptance of the study and its acceptance of data from comparable trials for other MBC therapies. Genentech took extensive steps between CDER's initial review of the E2100 study in 2006 and CDER's acceptance of the study in 2008 to address the issues CDER now resurrects:

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[39] EMA, Questions and Answers on the Review of Avastin (bevacizumab) in the Treatment of Metastatic Breast Cancer, Dec. 16, 2010, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/12/WC500099939.pdf (emphasis added). Indeed, rather than finding that AVADO and RIBBON1 undermine the evidence of Avastin's clinical benefit, the EMA concluded that RIBBON1 supports the additional approval of Avastin with capecitabine.

[40] Transcript, June 28, 2011 Public Hearing at 259:3-12 (statement of Dr. Pazdur).

- *Open-Label Design:* Multiple sensitivity analyses showed no evidence of bias in the E2100 tumor assessments, refuting CDER's concern with the study's open-label design.[41] This design is common in MBC: 78% of the ongoing phase 3 MBC trials on clinicaltrials.gov are open-label; Gemzar's approval was based on time to progression in an open-label study; and data from open-label studies have formed the basis of approval in breast cancer for Herceptin, Tykerb, and Ixempra.[42]

- *"Missing" Data:* The "missing" data in E2100 reflect 10% of patients who did not have scans for independent review, and 34% whose PFS results were censored in the primary analysis when there was no tumor assessment within three months of data cutoff. The 10% rate of missing scans is the same as seen in the pivotal study that supported the full approval of Tykerb for MBC.[43] CDER also accepted the Tykerb study with 31% of patients having data censored within 100 days of the database cutoff date. E2100 was thus in line with the amount of missing data in the Tykerb study, and in E2100 the frequency and reason for censoring, along with the number of missing scans, were balanced across the study arms. Importantly, several groups have recently recommended, on the basis of meta-analysis data showing little evidence for systematic bias, that blinded independent radiology reviews of a sample (subset) of cases would be adequate for an open-label or incompletely blinded trial.[44]

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[41] Transcript, June 28, 2011 Public Hearing at 234:8-14; PFS Is a Benefit 'in the Right Context,' Pazdur Says in Q&A on Avastin Approval, The Cancer Letter, Feb. 29, 2008 (quoting Dr. Pazdur: "[t]here was close agreement between investigator-assessed endpoints … and the independent radiographic facility (IRF)").

[42] Transcript, June 29, 2011 Public Hearing at 52:16-53:7; Genentech Presentation Slides, June 29, 2011 Public Hearing at 72; FDA Summary Bases of Approval (Drugs@FDA): Herceptin, Gemzar, Tykerb, and Ixempra.

[43] Transcript, June 29, 2011 Public Hearing at 55:12-21; Genentech Presentation Slides, June 29, 2011 Public Hearing at 77; FDA Summary Basis of Approval, Tykerb.

[44] Amit O, Mannino F, et al. Blinded independent central review of progression in cancer clinical trials: Results from a meta-analysis. Eur J Cancer 2011, doi:10.1016/j.ejca.2011.02.013; Dodd LE, Korn EL et al. An audit strategy for progression-free survival. Biometrics 2011, doi: 10.1111/j.1541-0420.2010.01539.x; Pignatti F, (continued…)

- *Assessment Variation:* Variation in radiology scan interpretation, and between the investigators and independent review facility, was similar to that in pivotal studies of other approved MBC therapies. Where two primary radiologists disagreed in scan interpretation, in 98% of the cases a third radiologist agreed with one of the primary radiology measurements.[45] The agreement rate of 49% between investigators and the independent review facility in disease progression status and date were nearly identical to those for the pivotal trials of Tykerb (52%) and Ixempra (51%).[46] Again, the discrepancy rates were equivalent by study arm in E2100, showing no evidence of bias. Most importantly, there was remarkable agreement between the IRF and the investigator-determined hazard ratios (0.48 and 0.42 respectively) and difference in median PFS (5.5 and 5.6 months respectively) for the E2100 study.

- *Random High:* In December 2010, CDER newly raised the question of whether the magnitude of effect seen in E2100 was an artificial "random high" because it was based on an interim analysis; after examining this issue in detail, Genentech found no evidence of bias. Extensive biostatistics literature shows that the potential for bias in a study like E2100, with a well-designed, pre-specified interim monitoring plan, is negligible.[47] Here, the absence of bias is seen in Genentech's calculations of adjusted estimates with commonly used methods, the tight confidence intervals for the PFS results in E2100, and the persistence of the magnitude of PFS

Hemmings R, Jonsson B. Is it time to abandon complete blinded independent central radiological evaluation of progression in registration trials? Eur J Cancer 2011, doi:10.1016/j.ejca.2011.05.009.

[45] Transcript, June 29, 2011 Public Hearing at 58:14-20; Genentech Presentation Slides, June 29, 2011 Public Hearing at 80. Any inter-reader variability that did exist likely created bias against the Avastin treatment arm. Transcript, June 29, 2011 Public Hearing at 59:7-15; Genentech Presentation Slides, June 29, 2011 Public Hearing at 81.

[46] Transcript, June 29, 2011 Public Hearing at 60:12-19; Genentech Presentation Slides, June 29, 2011 Public Hearing at 82.

[47] Transcript, June 29, 2011 Public Hearing at 61:3-62:1; *see, e.g.*, Freidlin B., Korn EL. Stopping clinical trials early for benefit: impact on estimation. Clin Trials 2009;6(2):119-125.

benefit from the first pre-planned interim analysis through 21 additional months of follow-up and more than 200 additional PFS events.[48]

In short, E2100 was well-designed and in line with the pivotal trials for other approved MBC agents. CDER approved Avastin in 2008 after carefully reviewing the E2100 study and expressing confidence about each of the points (apart from the "random high" point, which CDER did not even view as meriting consideration at approval) that it now cites as concerns:

> The current application demonstrates a robust effect on PFS and response rate. . . . Prespecified sensitivity analyses corroborate the maintenance of a treatment effect in handling missing data. Recent applications have had missing data similar to that observed in the current Avastin application . . . and [b]ecause of the close agreement between the two assessments (investigator, and IRF), systemic bias seems unlikely.[49]

CDER's 2008 determination still holds: E2100 was a reliable study that showed a clinically meaningful benefit for Avastin with paclitaxel.

C. The Data from the First-Line MBC Studies Support Paclitaxel as a Preferred Partner for Avastin.

The greater magnitude of effect observed with Avastin and weekly paclitaxel in E2100 relative to the effect in AVADO and RIBBON1 with non-paclitaxel chemotherapies suggests that weekly paclitaxel is a preferred chemotherapy partner with Avastin in first-line MBC. The data from these studies also offer a biological explanation for why paclitaxel would be a preferred partner – patients received greater exposure to both chemotherapy and Avastin when these two agents are used in combination.

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[48] Transcript, June 29, 2011 Public Hearing at 62:2-14; *see also* Discussion Paper: Response to the issue raised by FDA that the E2100 result may represent a "random high" (January 2011).

[49] Office Director's Memo, at 4-5.

Avastin in combination with paclitaxel results in a longer treatment duration than Avastin in combination with the other taxane docetaxel. The median treatment duration for Avastin in combination with paclitaxel in E2100 (8.4 months) was longer than that observed in combination with docetaxel in the AVADO and RIBBON1 studies (5.5 and 4.2 months, respectively).[50] Similarly, the proportion of patients on treatment at 12 months was 30% for Avastin with paclitaxel in E2100, compared to 0% and 8.5% for Avastin with docetaxel in AVADO and RIBBON1.[51]

These studies also indicate the superior tolerability of Avastin with weekly paclitaxel, which results in greater therapeutic exposure. CDER specifically identified greater overlapping toxicity as one of two potential bases for a chemotherapy-specific treatment effect,[52] and the data show this very difference. Dose intensity prior to progression of disease was greater in E2100 than in AVADO and RIBBON1 (100%, compared to 78% and 88%). Docetaxel chemotherapy was capped at nine cycles in the AVADO study, due to anticipated lack of tolerability for longer treatment. In RIBBON1, there was no cap on docetaxel, and the poorer tolerability of this agent was clear: there was more discontinuation due to toxicity prior to disease progression at ≥27 weeks for Avastin with docetaxel (59%) than with paclitaxel (27%).[53]

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[50] Transcript, June 29, 2011 Public Hearing at 46:9-17; Genentech Presentation Slides, June 29, 2011 Public Hearing at 62.

[51] Transcript, June 29, 2011 Public Hearing at 46:9-17; Genentech Presentation Slides, June 29, 2011 Public Hearing at 62.

[52] CDER, Summary of Arguments Supporting CDER's Proposal to Withdraw Approval of Avastin's Indication for the Treatment of Metastatic Breast Cancer (May 13, 2011) at 36.

[53] This observation is not contradicted by the experience with Avastin in other cancers, as suggested by CDER. For example, in metastatic colorectal cancer, the number of cycles of chemotherapy was not limited in the second-line setting, and in metastatic renal cell carcinoma, there was no chemotherapy partner. Thus these other indications are not relevant to this argument. In fact, the foundation of combination chemotherapy in cancer is based on clinical tolerability, which may limit dose intensity and planned or unrestricted duration.

These data – combined with the fact that the less intermittent nature of weekly paclitaxel compared to three-weekly docetaxel also may contribute to a better therapeutic effect – suggest that Avastin with weekly paclitaxel is more effective because it allows greater exposure (longer, more ideal dose intensity, and more frequent) to both a highly potent chemotherapy and the anti-angiogenic activity of Avastin. This is further supported by data in the second-line setting, which showed a larger magnitude of effect when Avastin was combined with paclitaxel compared with docetaxel (PFS hazard ratios of 0.59 vs. 0.76; OS hazard ratios of 0.68 vs. 0.86),[54] as well as by data from an Amgen study (which CDER referred to as Study 10) that showed an investigator-assessment hazard ratio for Avastin plus paclitaxel that is nearly identical to the one shown in E2100.[55] Notably, this subject of chemotherapy backbone, duration and schedule, and varying treatment outcomes was discussed in the American Society of Clinical Oncology (ASCO) 2011 Educational Session on "Targeting Angiogenesis in Breast Cancer," which involved presentations from four leading specialists.[56] The ASCO discussion highlights the potential importance of the chemotherapy partner.

These clinical data are consistent with preclinical findings. A uniform finding in

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[54] The PFS hazard ratio of 0.59 for the paclitaxel cohort in RIBBON2 is very similar to the PFS hazard ratio of 0.57 in E2100 when the same analytical approach is used (not censoring for non-protocol therapy). These cohort subgroups are small, and the data must be interpreted with caution, but they show a larger magnitude of effect for patients receiving paclitaxel compared to docetaxel.

[55] Study 10 is an Amgen-sponsored motesanib Phase II study that included an open-label arm in which patients received Avastin plus paclitaxel as an exploratory comparison. The Study 10 investigator PFS HR was 0.56 (95% CI 0.39, 0.80), compared to the E2100 investigator HR of 0.51 and the E2100 IRF HR of 0.57 when the same analytical approach was used (no censoring for non-protocol therapy).

[56] *See* Dickler MN, Kerbel RS, et al. Targeting Angiogenesis in Breast Cancer: Can Recent Clinical Trials Inform the Science and Future Clinical Trial Design. ASCO Educational Book 2011:26-32, *available at* http://www.asco.org/ASCOv2/Education+%26+Training/Educational+Book?&vmview=edbk_detail_view&confID=102&abstractID=1128.

animal models is that longer exposure to Avastin and chemotherapy increases efficacy.[57] Preclinical data also suggest that the schedule of chemotherapy administration may contribute to the combination's anti-angiogenic effects.[58] These observations further support the proposition that weekly paclitaxel is a preferred partner for Avastin in MBC.

CDER improperly dismisses this view as not definitively proven, partly by citing results from Study 10 that it had not reviewed in detail and in which the investigator PFS results were in fact similar to E2100.[59] CDER's current position is at odds with its own prior regulatory actions that distinguished between paclitaxel and other chemotherapy agents. Throughout the regulatory history of Avastin for MBC, CDER has treated each chemotherapy pairing with Avastin as distinct. In 2006, as Dr. Keegan admitted,[60] CDER specifically recommended that the RIBBON1 and RIBBON2 studies be powered to measure the potential different treatment effect

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[57] Bagri A, Berry L, et al. Effects of anti-VEGF treatment duration on tumor growth, tumor regrowth, and treatment efficacy. Clin Cancer Research (2010); 16(15):3887-3900; *see also* Transcript, June 29, 2011 Public Hearing at 45:12-15; Genentech Presentation Slides, June 29, 2011 Public Hearing at 61.

[58] Dickson PV, Hamner JB, et al. Bevacizumab-Induced Transient Remodeling of the Vasculature in Neuroblastoma Xenografts Results in Improved Delivery and Efficacy of Systemically Administered Chemotherapy. Clin Cancer Res 2007;13:3942-3950.

[59] Transcript, June 28, 2011 Public Hearing at 181:13-20. CDER conceded that it had not reviewed underlying data from the study, and insufficient data were available for regulatory decision-making. *Id.* at 238:13-240:9. As noted in the published version of the study, the different median PFS findings in the paclitaxel-only arms of Study 10 and E2100 may be "confounded by differences in patient demographics, tumour biology, size of the study, and baseline tumour burden." Martin M, Roche H, et al. Motesanib, or open-label bevacizumab, in combination with paclitaxel, as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Oncol 2011; 12:369-76, at 374.

Data that Amgen recently made available further indicate that estimation of the Avastin treatment effect in Study 10 is limited by the higher rate of early censoring in the paclitaxel plus placebo arm and the low number of IRF-assessed PFS events with likely informative censoring and wide confidence intervals for the estimated hazard ratio. June 28, 2011 Hearing Transcript at 186-87, 299-301. For this reason, there should be equal attention given to the investigator PFS results in Study 10, provided by Amgen, which had a higher number of PFS events and resulting higher precision, and which, as noted, showed PFS results that were highly similar to E2100.

[60] Transcript, June 28, 2011 Hearing at 255:2-256:4.

between the capecitabine and taxane/anthracycline comparisons. CDER's rationale was that "the treatment effect *will vary* according to the chemotherapy regimen used."[61]

CDER's approval of Avastin with paclitaxel in 2008 after having considered less favorable data from AVADO (Avastin with docetaxel) and the AVF2119g study (Avastin with capecitabine in the second and third-line settings) further shows CDER's acceptance of differences across chemotherapy agents. The AVADO PFS results CDER considered in 2008 showed a 0.8-month median PFS difference with docetaxel. The AVF2119g data showed an effect on objective response rate (ORR) but not a statistically significant effect on PFS for Avastin with capecitabine in the later-line setting. Having considered these data, CDER approved Avastin for use only with paclitaxel, implicitly recognizing that the chemotherapy partner affected the efficacy results observed in the different studies.

There is not a sound basis for CDER's denial now that the studies reflect a unique therapeutic profile for Avastin with weekly paclitaxel. The lack of pharmacokinetic data reflecting antagonism or synergism between Avastin and its chemotherapy partner is not dispositive, because the emerging explanation for a preferential effect with paclitaxel is that weekly paclitaxel allows greater clinical exposure to both Avastin and chemotherapy due to schedule and tolerability over time. This explanation is consistent with the foundation of combination chemotherapies in cancer, which is based on the clinical tolerability and dose intensity of effective agents rather than their pharmacokinetic interactions.

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

D. The Data from the First-Line Studies Support Avastin's Efficacy Against MBC.

CDER's improper rejection of a difference based on chemotherapy partners is coupled with a selective and unduly restrictive reading of the data from the other first-line studies. While these studies' lesser magnitude of median PFS difference indicates that the chemotherapy partner affects the magnitude of PFS effect, as predicted by CDER in 2006, the PFS hazard ratios from AVADO and RIBBON1 still show a robust reduction in the risk of disease progression or death. Specifically, there was a 38% reduction of risk in the standard-dose AVADO arm (HR 0.62, 95% CI 0.48, 0.79) (p=0.0003), 36% in the taxane/anthracycline comparison of RIBBON1 (HR 0.64, 95% CI 0.52, 0.80) (p<0.0001); and 31% in the capecitabine comparison of RIBBON1 (HR 0.69, 95% CI 0.56, 0.84) (p=0.0002). These hazard ratios are considered to be clinically meaningful, as reflected in the study designs and endorsement by study investigators and institutional review boards. They exceeded the hazard ratios that were targeted for these studies (25-30% risk reduction in PFS),[62] and are comparable to the PFS hazard ratios demonstrated for other agents commonly used in MBC (including Gemzar) and the magnitude targeted in ongoing NCI-sponsored trials in MBC. As Dr. O'Shaughnessy explained at the hearing, in first-line MBC a hazard ratio of 0.65 or 0.70 demonstrates "that treatment has perturbed the natural history of metastatic breast cancer."[63]

CDER placed little focus on these significant improvements in the hazard ratios, even though it agreed at the hearing that it is important to consider both the hazard ratios and

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[62] CDER acknowledged in response to a question from the Presiding Officer that studies are typically designed to target a particular hazard ratio. Transcript, June 28 Public Hearing at 303:11-304:10

[63] Transcript, June 29, 2011 Public Hearing at 160:16-22.

medians.[64] Given the strong risk reductions shown by Avastin across the MBC studies, CDER has unduly relied on the median PFS results in AVADO and RIBBON1 to conclude that these studies invalidate the results of E2100.

E. The Clinically Meaningful Effect of Avastin Plus Weekly Paclitaxel is Especially Pertinent to Aggressive Forms of MBC.

While the data support a clinically meaningful benefit of Avastin plus paclitaxel for first-line treatment of the overall population of patients with HER2-negative MBC, this benefit is especially compelling for patients who have the most aggressive forms of disease given their unique lack of other treatment options. For example, up to 24% of patients with invasive breast cancer have tumors classified as triple-negative (TNBC), and the prognosis for these patients is notably poorer than that of patients with non-TNBC tumors.[65] Median life expectancy for patients with newly diagnosed recurrent or metastatic TNBC is only 12-16 months,[66] whereas median life expectancy for the broader MBC population is 19 months or longer.[67]

In the face of the most aggressive forms of MBC, such as TNBC and hormone receptor-positive disease with unfavorable characteristics (*e.g.*, visceral disease, high tumor burden, and rapid disease progression), patients have limited therapeutic options. For example, there currently are no targeted therapies specifically available for patients with TNBC. Given the higher likelihood of early recurrence and poor outcomes associated with recurrent TNBC,

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[64] CDER agreed that hazard ratios have the advantages of reflecting the data for all patients in a trial across the full time course of the study and reducing bias through adjustment for prognostic factors. Transcript, June 28, 2011 Public Hearing at 241:8-242:19.

[65] Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease at 2-3. *See* Appendix C.

[66] *Id.*

[67] Piccart-Gebhart, MJ, Burzykowski T, et al. Taxanes Alone or in Combination With Anthracyclines As First-Line Therapy of Patients With Metastatic Breast Cancer. J Clin Oncol 2008;26(12):1980–1986.

patients with loco-regional TNBC typically are offered adjuvant chemotherapy, which limits these patients' treatment options if their disease recurs or becomes metastatic.[68] Also, these patients are able to receive fewer lines of therapy before their disease progresses to a point where treatment is no longer tolerable or effective. Hence the treatment of aggressive TNBC and hormone receptor-positive tumors are particularly acute unmet medical needs within MBC.

Avastin is an important treatment for patients with aggressive disease. In the United States, combination treatment often is recommended to achieve rapid control of these cancer phenotypes. Among the four most commonly used combination therapies for aggressive forms of MBC,[69] Avastin provides a notable rate and duration of disease control.[70] Indeed, the combination chemotherapy results are much more in line with AVADO and RIBBON1 than E2100 in terms of the efficacy they demonstrate. Reflecting this favorable efficacy profile relative to other cytotoxic combination therapies, Avastin plus paclitaxel has been widely adopted as an important treatment option for TNBC patients.[71]

Furthermore, it is meaningful that in E2100, the data for the subset of TNBC patients showed nearly a doubling in response rate (from 21.7% to 42.9%), a 5.3-month improvement in PFS (from 5.3 months to 10.6 months), with HR 0.49 (95% CI 0.34, 0.70), and a

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[68] Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease at 4. *See* Appendix C.

[69] Avastin + paclitaxel; Gemzar + paclitaxel; docetaxel + capecitabine; and ixabepilone + capecitabine.

[70] Genentech Presentation Slides, June 29, 2011 Public Hearing at 110.

[71] Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease at 4. *See* Appendix C.

12.5% between-arm increase (from 61.3% to 73.8%) in 1-year survival.[72] An overall survival trend was also observed in this group.[73]

At the same time, the safety experience for TNBC patients in E2100 and the other first-line MBC studies was consistent with the larger safety profile from these studies.[74] In comparison, significant toxicities are associated with the other chemotherapy doublets that are used for metastatic TNBC. These toxicities, including substantial increases in anemia, thrombocytopenia, stomatitis, hand-foot syndrome, and neuropathy, can be treatment-limiting and require frequent monitoring by physicians.[75] Relative to other combination therapies that are used to address these particularly challenging forms of MBC, Avastin thus offers substantial benefits, with comparable or lesser toxicity.

III. Avastin's Well-Understood and Unchanged Safety Profile Supports Maintaining Accelerated Approval.

CDER acknowledged without qualification that Avastin's safety profile is fairly described in its approved labeling and has not changed materially from the time of accelerated approval.[76] The parties disagree over whether this known safety profile is acceptable in light of the observed efficacy in this treatment setting, and over the safety issues with other agents patients will be required to take if Avastin is no longer available.

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[72] *Id.* at 5. Similar efficacy results – *i.e.*, improvements in PFS, 1-year survival, and objective response, with no detriment to overall survival – have been observed in TNBC patients enrolled in AVADO, and RIBBON1. *Id.* at 7.

[73] *Id.* at 5.

[74] *Id.* at 7-8.

[75] *Id.* at 10.

[76] Transcript, June 28, 2011 Public Hearing at 213:17-214:2.

A. There Were Fewer Deaths Among Avastin Patients than in Patients Not Taking Avastin.

Data presented at the hearing demonstrated that there were fewer total deaths, and no increase in treatment-related deaths, in patients treated with Avastin relative to patients treated with chemotherapy alone. CDER has focused repeatedly on individual deaths that it attributed to adverse events associated with Avastin, even though deaths due to the same adverse events occurred with chemotherapy alone.[77] To support this focus and argue for a safety concern, CDER has cited isolated case narratives taken only from the Avastin arms of the studies, rather than focusing on the totality of the data, despite CDER's concession at the hearing that a patient receiving Avastin over chemotherapy alone for MBC faces *no* increased mortality risk.[78]

The facts are clear. The pooled safety analysis of the first-line MBC studies[79] shows that there were fewer total deaths (52.0% vs. 55.8%) and fewer deaths from MBC (48.1% vs. 51.5%) in the Avastin arms compared to the chemotherapy-only arms. The occurrence of non-MBC deaths was similar (3.9% vs. 4.3%), and within these non-MBC deaths, the rate of

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[77] Transcript, June 28, 2011 Public Hearing at 224:3-227:21.

[78] *See, e.g.*, Transcript, June 28, 2011 Public Hearing at 226:9-11, 293:14-16, 294:5-9, 302:18-303:10. Most recently, CDER informed Genentech days before the close of the docket in this proceeding that it would be adding hundreds of pages of individual case narratives to the record, indicating that its primary focus was 12 mortality/Grade 4 adverse event narratives taken only from the Avastin arms. This selective use of case narratives can lead to bias in interpreting the benefit-risk for Avastin. Similar narratives appear in the chemotherapy-only arms, at slightly higher rates. In addition, it bears noting that, in attributing these deaths to Avastin, CDER has disagreed with several of the investigators who treated these patients and who did not consider these mortalities to be related to Avastin. Discussion Paper: Treatment-Related Mortality in the AVADO and RIBBON1 Studies at 1. *See* Appendix D.

[79] These data reflect the pooled analysis of 1,427 MBC patients who received the standard dose of Avastin.

treatment-related deaths was *identical* – 1.8% in the Avastin arms and 1.8% in the chemotherapy-only arms.[80]

Avastin's safety is further bolstered by the survival advantage seen for Avastin with paclitaxel in E2100 for up to 30 months of the observation period, when the survival curves then became superimposable.[81] In E2100, there was a 7.4% increase in survival at one year (95% CI 1.3%, 13.5%) and a 4.9% increase in survival at two years (95% CI –2.4%, 12.2%). Although E2100 did not demonstrate a statistically significant improvement in overall survival, these landmark survival data suggest that an improvement in survival is more likely than no improvement when Avastin is added to paclitaxel. CDER's 2008 Office Director memorandum cited these 1-year and 2-year survival rates as evidence that a detrimental effect on OS was unlikely[82] and as a counter to the mortality observed in the first study year.[83]

B. The Most Common Risks Are Manageable; Other Serious Adverse Events Occur Infrequently.

Hypertension and proteinuria account for all but 5.6% of the increase in Grade ≥3 adverse events seen with Avastin in the pooled safety analysis.[84] Physicians and patients must

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[80] Genentech Presentation Slides, June 29, 2011 Public Hearing at 18. For the E2100 study, there similarly were fewer total deaths (70.5% vs. 73.9%) and fewer MBC deaths (66.4% vs. 69.3%) on the Avastin arm, and similar rates of non-MBC deaths across the two arms (4.1% vs. 4.6%). A CDER *post hoc* assessment of treatment-related deaths found a 1.7% rate of treatment-related deaths in the Avastin arm compared to 0.3% in the paclitaxel-only arm, but as Genentech explained at the hearing, CDER was unable to conduct its *post hoc* assessment of the paclitaxel-only group, inevitably leading to higher rates in the Avastin group. Transcript, June 29, 2011 Public Hearing at 21:5-19. In AVADO, RIBBON1, and the pooled analysis, this aberrant finding vanishes. *Id.* at 22:7-10, 24:16-20; Genentech Presentation Slides, June 29, 2011 Public Hearing at 21.

[81] Dr. Joseph Sparano, Chair of the ECOG Breast Cancer Committee, emphasized in his hearing testimony that the early survival benefit seen in E2100 and the combined analysis with AVADO and RIBBON1 "provide[] irrefutable evidence of a favorable risk-benefit ratio." Transcript, June 28, 2011 Public Hearing at 53:6-14.

[82] Office Director's Memo at 3.

[83] *Id.* at 6.

[84] Genentech Presentation Slides, June 29, 2011 Public Hearing at 27.

give careful attention to these side effects, as directed in Avastin's labeling; but viewed in appropriate perspective, neither hypertension nor proteinuria justifies a negative determination of benefit-risk.

The pooled safety data show that there were no deaths due to hypertension, Grade 4 hypertension occurred in only 0.4% of Avastin-treated patients (5 patients out of 1,427), and there was little treatment discontinuation due to hypertension (1.7%).[85] Doctors are experienced with managing hypertension, given its prevalence,[86] and have well-established treatment guidelines for the condition. As a special National Cancer Institute Angiogenesis Task Force recognized in its 2010 recommendations,[87] VEGF inhibition-induced hypertension is considered reversible, such that discontinuation or dose reduction are means of control; and physicians are advised to anticipate discontinuing or reducing anti-hypertensives when VEGF inhibition treatment ends.[88]

Proteinuria is also well-described in the package insert, which includes guidelines for monitoring and management. The pooled safety data show no deaths due to proteinuria in the first-line MBC studies. Grade 4 toxicity (clinical nephrotic syndrome) occurred in 0.4% of

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[85] Genentech Presentation Slides, June 29, 2011 Public Hearing at 31.

[86] 50 million Americans – nearly one in three over the age of 18 – have hypertension warranting treatment. Half of the U.S. population over age 60 is hypertensive, and two-thirds of these individuals require more than one drug to manage their condition, a level of hypertension similar to the definition of Grade 3 hypertension used in AVADO and RIBBON1. National Heart, Lung, and Blood Institute, National Institutes of Health, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Aug. 2004).

[87] Maitland ML, Bakris GL et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 2010;102(9):596-604; *see also* Genentech Presentation Slides, June 29, 2011 Public Hearing at 30.

[88] CDER's reliance on the meta-analysis by Rampura *et al.* as evidence that Avastin causes an increase in the risk of severe or life-threatening hypertension is misplaced. Transcript, June 28, 2011 Public Hearing at 195:16-196:4. This meta-analysis considers both approved and non-approved indications, and there is considerable heterogeneity in the methodology of each included study. The meta-analysis does not take into account study design, differences in adverse event reporting, and adjustment for treatment exposure. These limiting factors tend to bias the results.

Avastin-treated patients (5 of 1,427 study participants), treatment discontinuation due to proteinuria was low (1.1%), and proteinuria was not associated with a reduction in glomerular filtration as determined by serum creatinine.

CDER's citation of proteinuria data in the Avastin package insert from a trial in patients with renal cell carcinoma (RCC) is misplaced, because patients with RCC face increased risk from proteinuria.[89] Pre-clinical and clinical data indicate that massive proteinuria occurs in patients with pre-existing kidney disease, such as after nephrectomy, where repair and resolution may take longer. In the RCC trial that CDER referenced, all but two of the 649 patients in the trial had a full or partial nephrectomy. The higher incidence of proteinuria and its consequences in RCC patients reflect the nature of that disease and do not directly apply to MBC patients.[90]

New data from the adjuvant colon cancer study C-08, conducted by the NSABP and supported by Genentech, provide further reassurance regarding the reversibility of Avastin-associated hypertension and proteinuria. At the 2011 ASCO meeting, the C-08 investigators presented data on the incidence of Grade ≥3 hypertension and proteinuria after the end of Avastin treatment. During the study, the incidences of Grade ≥3 hypertension and proteinuria

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[89] CDER Summary of Arguments at 43-44.

[90] At the hearing CDER cited a meta-analysis by Wu *et al*. regarding the risk of severe or life-threatening proteinuria. Transcript, June 28, 2011 Public Hearing at 192: 22-193:13. In this meta-analysis, a disproportionate number of events occurred in patients with renal cell carcinoma (with pre-existing decreased renal function); however, the overall results from the meta-analysis are in line with Avastin's approved prescribing information. CDER also cited a meta-analysis by Izzedine *et al.* regarding pathological findings, specifically thrombotic microangiopathy, in renal biopsy specimens. *Id.* at 194:7-195:5. Notably, thrombotic microangiopathy is seen in association with pre-eclampsia, a VEGF-mediated disorder that reverses with delivery of the placenta, usually without residual kidney disease. Of the 8 cases discussed by CDER from this meta-analysis, 7 patients had pre-existing decreased renal function (e.g., renal cell cancer, diabetes, prior nephrectomy, chronic kidney disease, prior treatment with nephrotoxins like cisplatin or gemcitabine). Importantly, as noted in Genentech's presentation at the hearing, the data from NSABP C-08 in 2,700 patients demonstrates that the resolution of proteinuria on the Avastin-treated arm is indistinguishable from the chemotherapy alone arm.

were consistent with the Avastin label.[91] Within 12 months of completing treatment, essentially no differences were observed between the arms for Grades 3 and 4 adverse events: Grade ≥3 hypertension was observed in 0.7% versus 0.6%, and Grade ≥3 proteinuria in 0% versus 0.1%, in the Avastin and chemotherapy arms.[92]

Aside from hypertension and proteinuria, the remaining 5.6% of the 13.3% overall increase in Grade ≥3 select adverse events is attributable to a range of other causes which, individually, occurred infrequently in absolute terms and showed small absolute increases in the pooled analysis.[93]

These data reflect the experience of physicians and patients who have used Avastin and found the safety profile to be largely manageable. At the hearing, MBC patient Priscilla Howard testified: "As with all medications, there are side effects to Avastin. However, my doctors have been able to keep those side effects at bay while continuing my treatment."[94] And patient Elizabeth Cleary described her experience with the side effects of Avastin relative to those she experienced with other treatments:

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[91] Grade ≥3 hypertension occurred at 12% in the Avastin arm compared to 1.8% in the chemotherapy arm; and grade ≥3 proteinuria occurred at 2.7% in the Avastin arm compared to 0.8% in the chemotherapy arm. Genentech Presentation Slides, June 29, 2011 Public Hearing at 36.

[92] Genentech Presentation Slides, June 29, 2011 Public Hearing at 36.

[93] For example, the rates of bleeding in the Avastin vs. the chemotherapy-only arm were 1.6% vs. 0.4%, for arterial thromboembolism were 1.9% vs. 0.3%, for gastrointestinal perforation were 0.5% vs. 0.3%, and for fistula were 0.4% vs. 0.3%. Venous thromboembolism occurred more frequently in the chemotherapy arm: 3.8% vs. 3.0% in the Avastin arm. A reversible toxicity unique to Avastin that CDER has highlighted in public communications, reversible posterior leukoencephalopathy syndrome, occurred in only one of the 1,427 Avastin-treated patients.

[94] Transcript, June 28, 2011 Public Hearing at 29:5-8.

> So for now, I live with hypertension. It requires two prescription medications to manage. In the past when I was on chemotherapy, I used a combination of eight prescription medications, eight over-the-counter medications, multiple noninterfering supplements and several topical treatments just to tolerate the side effects of chemotherapy. That difference alone applies directly to my ability to live fully as I have been able to do for the past four and one-half years.[95]

Oncologists experienced with the use of Avastin in MBC also attested to Avastin's tolerability. As Dr. Waintraub described: "Aside from the easily controllable hypertension and occasional nosebleeds, the patients on Avastin have tolerated extremely well."[96] Dr. John Powderly a medical oncologist similarly noted:

> Oncologists are well versed in managing Avastin and its side effects. We use it for the other FDA on label indications of colon, lung, renal and brain tumors, and it's been used off label per NCCN guidelines for ovarian and melanoma. CDER argues that the drug is too toxic, but oncologists are well aware it potentiates chemotherapy and has unique vascular complications. We minimize the risk of these complications by controlling the dose, decreasing the dose where appropriate in chemotherapy, or even rolling Avastin with second or third cycles so it's safer. We manage the hypertension, and we manage the proteinuria.[97]

These views are not merely anecdotal. Extensive clinical data and experience show that the safety of Avastin in MBC is manageable. As the E2100 investigators, who are leading breast cancer oncologists, concluded in their study publication: "Most toxic effects were minimal, rarely limited therapy, and did not have a detrimental effect on overall quality of life."[98]

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[95] Transcript, June 28, 2011 Public Hearing at 43:16-44:3.

[96] *Id.* at 51:5-7.

[97] *Id.* at 60:10-61:1.

[98] 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, at 2673.

C. Other Treatment Options Present Serious Risks with Limited Efficacy.

The acceptability of Avastin's safety profile becomes especially clear when viewed in comparison to other MBC treatments, a comparison CDER does not appear to have undertaken. Even with single chemotherapy agents, such as paclitaxel and docetaxel, the occurrence of multiple, serious adverse events associated with cytotoxic therapies is well-established, including kidney, liver, cardiac, respiratory, and other toxicities. CDER highlighted Avastin's black box warning during the hearing proceedings, but it failed to mention that most MBC treatments (Taxol, Taxotere, Abraxane, Ixempra, Xeloda, Herceptin, Tykerb) also have black box warnings, and that other products such as Gemzar have their own serious risks.

When Gemzar – the only other agent with a first-line approval that includes HER2-negative MBC – is added to paclitaxel, an increase in adverse events is observed due to both overlapping and additional toxicities, including Grade ≥3 neutropenia (35.4%), thrombocytopenia (5%), dyspnea (1.9%), anemia (4.3%), and transaminitis (5%).[99] Gemzar's labeling warns of severe and uncommon toxicities, including pulmonary toxicity such as adult respiratory distress syndrome, hemolytic uremic syndrome, and/or renal failure leading to death or requiring dialysis, severe and/or fatal hepatotoxicity, peripheral vasculitis and gangrene, congestive heart failure, severe skin toxicity, and toxicity related to infusion time and dosing frequency. The labeling also emphasizes the importance of monitoring for dose-limiting myelosuppression, renal dysfunction, and liver dysfunction. The limited use of Gemzar in clinical practice can be attributed, in part, to its toxicities and modest efficacy.[100]

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[99] Genentech Presentation Slides, June 29, 2011 Public Hearing at 40.

[100] 2010 ASCO Annual Meeting, Breast Cancer Track, Controversies in the Management of Metastatic Breast Cancer Education Session. Clifford Hudis, M.D., Chair and Speaker (noting that Gemzar has had limited uptake (continued…)

The use of anthracycline-based chemotherapy as a treatment option also presents serious safety concerns. The most commonly observed toxicities of anthracycline-based chemotherapy include hematologic adverse events such as neutropenia, anemia, and thrombocytopenia, and non-hematologic events such as nausea, vomiting, stomatitis, fever, diarrhea, infection, asthenia, and less frequently, cardiac dysfunction.[101] Cardiac toxicity is a well-recognized, cumulative dose-related serious safety event associated with anthracyclines, which limits a patient's lifetime exposure to the drug.[102]

These adverse events associated with other MBC therapies demonstrate that while Avastin's risk profile is distinct from that of other treatments for MBC, the overall degree of risk is at least comparable. CDER and the ODAC did not address at the hearing the toxicities associated with the other treatment options that patients will have to consider if Avastin is not available.[103]

Without the PFS benefit from Avastin combined with paclitaxel, patients will also face disease progression earlier and have to incur toxicities as they go on additional treatments. For instance, the E2100 safety data capture the toxicity of Avastin with paclitaxel (including an

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likely as the result of toxicity and other factors, including that the Gemzar study participants were not pretreated with taxanes, whereas currently many patients have been pretreated with taxanes).

[101] In a study comparing doxorubicin and paclitaxel versus fluorouracil, doxorubicin and cyclophosphamide (FAC) in women with first line MBC, high rates of toxicities were observed in the FAC group: 65% neutropenia (Grade 3 and 4); 19% nausea/vomiting (Grade 3 and 4); 7% anemia (Grade 3 and 4); 4% fever (Grade 3 and 4); and 7% on-study LVEF dysfunction, with 13% in follow-up (< 50%). Jassem J, Pieńkowski T, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol 2001;19(6):1707–1715.

[102] Smith LA, Cornelius VR, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomised controlled trials. BMC Cancer 2010;10:337; Jones RL, Swanton C, Ewer MS. Anthracycline cardiotoxicity. Expert Opin. Drug Saf. 2006;5(6):791-809.

[103] Dr. Pazdur referred briefly to the lack of a black box warning in the context of explaining CDER's thinking about the benefit-risk profile of Gemzar. Transcript, June 28, 2011 Public Hearing at 251:10. However, neither he nor any other CDER representative analyzed the risks associated with Gemzar in greater detail to explain how CDER weighs the risks of Gemzar plus paclitaxel relative to those of Avastin plus paclitaxel.

increase in neuropathy attributed to longer paclitaxel duration) over the 11.3-month median PFS interval, but captured the toxicity of paclitaxel alone over only a 5.8-month median PFS interval. Additional adverse events related to second-line treatment on the paclitaxel arm over the 5.5-month difference were not recorded, but almost certainly exist for the majority of patients. Both of these considerations – toxicities of alternative treatments or later-line treatments used at an earlier time – are essential to a fair assessment of the safety of Avastin. Neither consideration was addressed by CDER, yet both considerations support Avastin's favorable benefit-risk profile.

IV. The Accelerated Approval Statute and the Scientific Data Support Genentech's Middle-Ground Proposal.

This matter presents a serious choice: retain approval for women who will otherwise lose a valuable treatment option, in the face of CDER's questions about the magnitude of Avastin's benefit; or withdraw approval for a medication that a large portion of the medical community believes provides meaningful benefit to patients with a severe disease and limited treatments alternatives. Genentech has responded to this challenge by presenting the Commissioner with an option that addresses CDER's concerns while acting in the best interest of the public health: retain approval based on the unchanged finding of clinical benefit and safety in E2100; conduct a confirmatory trial with paclitaxel to replicate the magnitude of benefit seen in E2100, with continued approval hinged on the results of this trial; and adopt revised labeling and a further communication plan regarding the benefits and risks of Avastin.

A. Genentech's Proposal Addresses CDER's Concerns.

At the July 2010 ODAC, CDER made clear for the first time that it was seeking replication of the magnitude of median PFS benefit from E2100. Genentech responded to CDER's views by developing plans for a true confirmatory trial of E2100. This confirmatory

trial would examine Avastin with weekly paclitaxel and be powered to detect the magnitude of median PFS improvement seen in E2100. At the June 2011 hearing, Genentech proposed two further steps to address CDER's concerns while also meeting Genentech's "primary objective [of] preserv[ing], in an appropriate manner, options for women with metastatic breast cancer."[104]

First, Genentech stated its willingness to adopt restricted labeling to limit Avastin's use to those situations where the unmet medical need is most acute. Proposed labeling on this point is attached as Appendix A. CDER did not respond to the core basis for this restricted labeling proposal: the lack of treatment options and uniquely severe, and undisputed, unmet need for patients with TNBC or hormone receptor-positive disease characterized by aggressive features, *e.g.*, by visceral metastases, high tumor burden, or rapidly progressive disease.

Genentech's second proposal is to implement a REMS focused on an enhanced communication plan and a patient Medication Guide to support informed treatment decisions by physicians and patients. The communication plan will inform physicians through a Dear Healthcare Professional Letter and an Avastin MBC Healthcare Professional Training Guide about the efficacy data on Avastin with paclitaxel, the differing effects seen with other chemotherapy partners, and important safety considerations. The Medication Guide will advise patients directly about the serious risks of Avastin, and will also inform them about the lack of overall survival and quality of life data. Further details on the Communication Plan and Medication Guide proposal are set forth in Appendix B.

[104] Transcript, June 29, 2011 Public Hearing at 104:21-105:2.

Genentech is also open to discussing limitations on its marketing of Avastin for MBC. If Avastin's approval is retained, Genentech sees an important need to educate prescribers on the current data and new labeling through its field personnel and other outreach. In conducting such activities, Genentech would submit all breast-cancer-related promotional pieces to CDER's Division of Drug, Marketing, Advertising and Communications in accordance with the accelerated approval procedures, and await advisory comments prior to their use.

Genentech's proposal directly addresses CDER's concerns about the balance of benefits and risks by focusing Avastin's approved use and labeling on those patients with the fewest available treatment options. These patients have the greatest unmet medical need, and present the most favorable benefit-risk profile for Avastin with paclitaxel due to the lack of viable alternative therapies.

B. Retaining Approval Is Consistent with the Law and the Science.

CDER acknowledged its discretion under the law to retain accelerated approval, even if it concluded that the confirmatory trials did not confirm clinical benefit. This acknowledgement is consistent with the accelerated approval provisions in the statute and regulations – which state that FDA *may* withdraw approval[105] – and with CDER's longstanding views on its discretion. For example, the Department of Health and Human Services (HHS) emphasized the need to act cautiously in withdrawing accelerated approval in responding to a U.S. Government Accountability Office report, stating that "[f]ailure to confirm clinical benefit in a completed trial . . . may reflect, for example, unforeseen limitations in trial design, rather

[105] FDCA § 506(b)(3)(B), 21 U.S.C. § 356(b)(3)(B); 21 C.F.R. § 601.43(a)(1) (emphasis added).

than clear evidence of lack of effectiveness."[106] When trials "do not appear to confirm clinical benefit, FDA must carefully assess each case, and consider the underlying reasons and the consequences of all regulatory options, including their potential impact on patients."[107] As HHS emphasized, "in addition to withdrawal of approval, FDA has other regulatory tools that can be considered and applied as appropriate."[108]

The facts here particularly support the exercise of this discretion:

- Avastin addresses a significant unmet medical need and is a valuable treatment option for MBC. Only one other non-hormonal treatment is specifically approved for first-line treatment encompassing HER2-negative disease – Gemzar – and the Gemzar data are weaker than those seen in E2100. Patients with aggressive forms of MBC face even poorer prognoses, have fewer treatment options, and represent a greater unmet medical need.

- The post-approval trials continue to demonstrate that Avastin provides clinical benefit in first-line MBC, with each meeting its agreed-upon primary endpoint. The smaller median PFS effect seen in these trials, when Avastin was combined with chemotherapies other than paclitaxel, can reasonably be attributed to a difference based on the chemotherapy partner.

- Avastin's safety profile is well-characterized, accurately described in the approved prescribing information, and not uniquely toxic compared to other therapies. The confirmatory studies have not identified any new safety signals.

- Genentech completed the post-approval studies with rigor and diligence.

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[106] 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 (Sept. 2009), App. V, FDA Comments on GAO Report, at 3.

[107] *Id.*

[108] *Id.* at 4. CDER's Dr. Robert Temple echoed this point at the first ODAC discussing the accelerated approval program in 2003: "when a drug has proved active … you don't lightly remove it because a trial failed to show overall survival effect. It's pretty obvious that you don't withdraw an active drug lightly. You try to do other studies." Transcript, March 12, 2003 ODAC at 49. Dr. Pazdur similarly emphasized, at this same 2003 hearing, that the accelerated approval regulations provide the agency judgment so the agency doesn't "need to have a reflex situation. You fail therefore you must come off." Transcript, March 12, 2003 ODAC at 131.

- The confirmatory studies were selected without the knowledge that CDER would require replication of the magnitude of median PFS benefit in E2100, based on CDER's guidance that the magnitude of benefit may vary with chemotherapy regimen, and with CDER's knowledge that the agreed upon confirmatory trials – first AVADO and later RIBBON1 – would not show the same magnitude of median PFS benefit as seen in E2100. This history explains the unique unforeseen circumstances present here that justify a new confirmatory trial with paclitaxel.

The only basis that CDER raises for withdrawal on these facts is the concern that the benefit seen in the confirmatory trials was smaller than in E2100. Withdrawal is not appropriate where there is demonstrated benefit, no new safety signals, a reasonable alternate explanation for the lesser effect on median PFS (that the choice of chemotherapy partner affects the level of benefit), and a means of testing that explanation through a further trial.

The only open question is whether the magnitude of benefit observed in E2100 will be confirmed in a new study of Avastin with paclitaxel. Given the rigor of review of the E2100 data, the meaningful probability that the chemotherapy partner has an impact on the magnitude of benefit, and the feasibility of a new study with paclitaxel, accelerated approval should be maintained pending completion of the study. Withdrawal on these facts would fundamentally undermine the goals of the accelerated approval program by prematurely and unnecessarily depriving patients and physicians of a treatment choice where the safety profile is unchanged and well-characterized, the confirmatory trials were positive, and a viable study could more definitively confirm clinical benefit.

FDA has previously exercised discretion to not withdraw accelerated approval under far less compelling facts:

- FDA permitted additional confirmatory trials after the initial confirmatory study for Erbitux® (cetuximab) failed to meet its primary endpoint of overall survival, which the sponsor attributed to the high percentage of patients in the control arm

who received post-progression treatment of Erbitux. In May 2010, FDA agreed that data from three additional studies could support full approval.[109]

- FDA exercised regulatory flexibility to permit additional confirmatory studies after the initial trials failed to confirm midodrine's benefit. The sponsor encountered considerable difficulty enrolling the required confirmatory study and terminated the study. In August 2010, 14 years after granting accelerated approval, FDA issued a notice of opportunity for a hearing on a proposal to withdraw approval.[110] However, FDA has not moved forward on withdrawal, and in January 2011 opened a public docket to facilitate communication regarding potential confirmatory studies or existing data that verify midodrine's benefit.[111]

- FDA granted full approval for doxorubicin for the treatment of AIDS-related Kaposi's sarcoma 12 1/2 years after initially granting accelerated approval. After the required confirmatory study was confounded by the introduction of highly active anti-retroviral therapy into clinical practice, FDA and the sponsor discussed designs for additional studies.[112] Ultimately, FDA granted full approval based on the reanalysis of the confirmatory study, a later ECOG trial, and published literature.

The facts regarding Avastin in MBC are more supportive of regulatory discretion.

C. Genentech's Proposed Confirmatory Study Can Provide Timely Results.

Genentech has addressed the feasibility of the confirmatory trial and the steps it will implement to facilitate prompt regulatory action. The trial is designed to allow withdrawal if interim study results indicate that the trial likely will not confirm the magnitude of Avastin's clinical benefit as evidenced by E2100 trial data.

As described at the hearing, the confirmatory trial will target a study population of 480 patients with HER2-negative MBC who have not received prior chemotherapy for metastatic disease. Randomization will be stratified by plasma VEGF-A level, prior adjuvant therapy use,

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[109] Transcript, Feb. 8, 2011 ODAC at 69-80.

[110] Proposal to Withdraw Marketing Approval; Notice of Opportunity for Hearing (Aug. 16, 2010), Docket No. FDA-2007-N-0475-0019.

[111] Trials to Verify and Describe Clinical Benefit of Midodrine Hydrochloride; Establishment of Public Docket, 76 Fed. Reg. 1620 (Jan. 11, 2011) (Docket No. FDA-2010-N-0637).

[112] Transcript, March 12, 2003 ODAC at 83-95.

and hormonal receptor status. Treatment regimens of the study are identical to E2100, with standard 3-weekly out of 4 weeks paclitaxel and Avastin continued until progression and with no built-in crossover (as was the case in AVADO and RIBBON1).

The study has two co-primary objectives: PFS in all patients, and PFS in patients with high plasma VEGF-A. Overall survival, 1-year survival, and response rate would be secondary endpoints. The study size would target 326 PFS events, which provide 85% and 99% power to detect a hazard ratio of 0.67 or 0.5 respectively.

The primary objective of the study is to confirm the magnitude of benefit seen in E2100 when Avastin is combined with weekly paclitaxel. A secondary key objective of the study is to validate a method of selecting patients who may derive a more substantial clinical benefit with Avastin using plasma VEGF-A. Recent data from AVADO, as presented by the investigators at the December 2010 San Antonio Breast Cancer Symposium, suggest that plasma VEGF-A may be a potential predictive marker for Avastin activity. Patients in AVADO with high levels of VEGF-A had a PFS hazard ratio of 0.49 (standard dose), whereas patients with low levels of VEGF-A had PFS hazard ratio of 0.86. This finding suggests that patients with high levels of VEGF-A may be more likely to derive a more substantial benefit from Avastin.[113]

Genentech met with CDER this February to review the study's design. At this Type B meeting, CDER confirmed that PFS results showing the same magnitude of median PFS difference as in E2100, without a detriment to OS, would support full approval with paclitaxel.[114]

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[113] Miles DW, de Haas SL, Dirix L, et al. Plasma biomarker analyses in the AVADO Phase III randomized study of first-line bevacizumab + docetaxel in patients with human epidermal growth factor receptor (HER) 2-negative metastatic breast cancer [abstract]. SABCS, *available at* http://www.abstracts2view.com/sabcs10/view.php?nu=SABCS10L_939&terms (last visited August 3, 2011).

[114] Minutes, Type B Meeting Feb. 22, 2011 at 5.

At the hearing, Genentech addressed CDER's concerns about study feasibility:

- *Enrollment Timing:* Genentech expects enrollment to start in the first quarter of 2012.

- *Prompt Action on Study Results:* Genentech will perform a prespecified interim PFS analysis. This early analysis could trigger an early voluntary withdrawal of accelerated approval if the futility boundary is crossed. Genentech discussed this analysis being conducted roughly three-and-a-half years after the study's start, although its post-hearing third-party feasibility assessment indicates that this analysis could occur at 2.6 years.[115]

- *Patient Enrollment:* The study will include sites in the United States, but Genentech expects (based on its prior Avastin study experience and a country-specific survey Genentech has already conducted) the study to be enrolled largely outside of the United States. U.S. enrollment will be driven by interest in the biomarker component and by those patients and physicians who are near equipoise on the Avastin data. Enrollment in the roughly 50 participant countries outside the U.S. will be driven by the fact that Avastin reimbursement and funding is limited in many countries outside the United States.[116]

- *Broad Experience:* Genentech has substantial experience in recruiting global trials and has successfully enrolled 10 Phase III Avastin breast cancer trials with 15,574 patients.

In short, Genentech demonstrated that the study is feasible and can be conducted in a manner consistent with maintaining access for women who benefit from Avastin while ensuring prompt action if the study fails to confirm the benefit of Avastin with weekly paclitaxel.

D. NCCN's July 2011 Reaffirmation Supports the Need for Accompanying FDA-Approved Prescribing Information.

Just over two weeks after the ODAC's negative vote, NCCN reaffirmed that Avastin "in combination with paclitaxel is an appropriate therapeutic option for metastatic breast

[115] For a sample size of 480, time to final PFS data availability would be 3.4 years from first patient enrolled (currently projected in Q1 2012). Mature survival data would be available 7.3 years from first patient enrolled.

[116] Even in Western Europe, access is limited in some countries such as the United Kingdom or parts of Spain due to funding restrictions.

cancer with the evidence designation 2A."[117] NCCN supported this recommendation with the view of the science that EMA and other regulators have endorsed: "The time to progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel."[118] Similarly, on the day after the FDA hearing, CMS announced that at the present time Medicare would continue to cover Avastin for MBC.[119]

The NCCN's recent endorsement of Avastin with paclitaxel underscores the scientific support for Avastin in MBC and increases the possibility that private and public payers will continue to reimburse the use of Avastin in MBC. This makes it even more essential to the public health that there be FDA-approved labeling to support the informed use of Avastin.

V. The ODAC Vote Should Not Prevent Continued Accelerated Approval.

The Commissioner should not give undue weight to the negative votes of the ODAC panel in resolving the issues before her. As their deliberations made clear, the ODAC panelists' conclusions rested on their preexisting views,[120] not a considered analysis of the data in light of the presentation of new data and new questions addressed at the hearing. Moreover, several ODAC members applied an incorrect efficacy standard, and the ODAC's lack of clinical

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[117] Press Release, National Comprehensive Cancer Network, NCCN Breast Cancer Panel Reaffirms Current Position And Recommendation Regarding The Use Of Bevacizumab In Metastatic Breast Cancer (July 19, 2011).

[118] *Id.*

[119] *See* Anna Yukhananov and Alina Selyukh, Medicare Will Keep Covering Roche's Avastin, Reuters, June 30, 2011; Andrew Pollack, Will Pay For Avastin In Treating Breast Cancer, New York Times Prescriptions Blog (June 30, 2011).

[120] Five of the six ODAC members who voted in favor of withdrawal served on the July 2010 ODAC panel. In that capacity, they evaluated the same dataset, reviewed nearly identical issues, and voted to withdraw Avastin's MBC indication. One member has considered and voted against Avastin's MBC indication on three occasions: at the December 2007 ODAC, the July 2010 ODAC, and, most recently, at the June 28-29, 2011 hearing.

Certain members appeared to express settled views on these questions before the presentations were completed. On the first day, before Genentech had an opportunity to make its presentations, one member challenged the quality of care provided to the numerous patients who testified that they benefited from Avastin: "[I]f they're being told by their doctors that their excellent outcome is being driven by this combination rather than by the chemotherapy drug, I'm not sure that they're being well served." Transcript, June 28, 2011 Public Hearing at 302:6-13.

experience with breast cancer and Avastin limited its ability to assess the medication's benefit-risk profile.

A. The ODAC Panel Did Not Apply the Correct Efficacy Standard.

Genentech and CDER agree that PFS constitutes a direct clinical benefit sufficient to support full approval for oncology medications.[121] Nonetheless, ODAC premised its vote on a rejection of PFS as a stand-alone measure of clinical benefit. Three comments are instructive:

- "I define efficacy in this setting as progression-free survival of significant magnitude coupled with a quality of life advantage or an overall survival advantage, and Avastin didn't achieve either of those definitions of efficacy."[122]
- "Drug approvals based on progression-free survival as a primary endpoint take us down a slippery slope, as we've seen in this meeting, for a number of reasons."[123]
- "I hear people keep talking about no impairment of overall survival, but what matters to patients is improvement in overall survival."[124]

These comments reflect a longstanding ODAC aversion to PFS as a clinical endpoint in first-line MBC, dating back to the December 2007 ODAC on Avastin's MBC indication.[125]

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[121] The FDA endorsed this view at the hearing, just as it did in originally approving Avastin, in approving Gemzar based on a similar metric, and as it has stated in a final Guidance. *See* Transcript, June 28, 2011 Public Hearing at 176:18-177:2 (observing that clinical benefit could be confirmed through replication of E2100 PFS results); Minutes, Feb. 26, 2009 Type B Meeting at 7 (requiring "demonstrated improvement in progression-free survival and evidence that survival is not impaired"); FDA, Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007) at 8.

[122] Transcript, June 29, 2011 Public Hearing at 237:19-238:3.

[123] *Id.* at 213:1-13.

[124] *Id.* at 175:2-6.

[125] *See, e.g.*, Transcript, Dec. 5, 2007 ODAC at 199:7-11 (defining "meaningful treatments for metastatic disease" as "overall survival and an increase in quality of life"). Other members of the June 28-29 panel offered similar views at the July 2010 ODAC. *See, e.g.*, Transcript, July 20, 2010 ODAC at 203:12-18 ("I voted no. . . . These progression-free survival still didn't translate to an improvement in overall survival or any type of patient-reported outcome improvement."); *id.* at 202:16-21 ("I just felt like with a surrogate endpoint like progression-free survival the burden of proof needs to be -- or the bar needs to be fairly high especially when you have concerns about toxicity and not necessarily demonstrated safety in terms of survival.").

The refusal by key ODAC members to embrace FDA's judgment that PFS improvement demonstrates clinical benefit necessarily undermines their votes. Indeed, given CDER's admission that *no* HER2-negative first-line treatment has shown a quality of life or overall survival benefit[126] – which reflects the challenges of demonstrating these measures in first-line MBC – ODAC's position risks barring any MBC approvals.

B. The ODAC's Deliberations Reflected a Lack of Relevant Clinical Experience.

Prior to the hearing, Genentech expressed concern about the composition of the ODAC panel, which included oncologists, statisticians and a patient representative – all without meaningful current clinical experience in breast cancer treatment.[127] Genentech recognized the qualifications of these individuals in their respective fields, but noted that breast oncologists with experience with Avastin would be best situated to consider the Avastin MBC data in context with their real-world experience treating MBC patients.

The final composition of the ODAC panel for the hearing included only six voting members, an unusually small size that required a special quorum waiver from the Commissioner. There were only two medical oncologists and no breast cancer specialists, as CDER's Director acknowledged after the hearing,[128] the panelists had little expertise with solid tumors, and no panel member cited direct clinical experience with Avastin. This absence of a real-world

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[126] Transcript, June 28, 2011 Public Hearing at 221:1-6; 252:11-15.

[127] Letter from Michael S. Labson, Covington & Burling LLP to Laurie Lenkel, Director, Office of the Ombudsman, FDA, Mar. 10, 2011; Submission of Genentech, Inc. in Response to the Food and Drug Administration's Notice of Opportunity for Hearing, Jan. 16, 2011 at 39-40.

[128] PDUFA V: Medical Innovation, Jobs, and Patients: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce (July 7, 2011) (statement of Dr. Janet Woodcock) ("I agree, there was no breast cancer expert, to my knowledge, on that panel."). The two ODAC members trained in medical (adult) oncology specialize in hematologic malignancy.

understanding of Avastin's effect in first-line MBC, and the underlying disease of breast cancer itself, was evident throughout the hearing.

For example, the ODAC's deliberations did not reflect the perspectives of patients and breast oncologists on Avastin's role in responding to the high unmet medical need in MBC. As the public testimony established, the unmet medical need in MBC is especially significant for patients with aggressive forms of disease for whom other therapies are not appropriate.[129]

In this setting of unmet medical need, delaying disease progression is not, as one ODAC member suggested, merely a "Pyrrhic" victory.[130] For symptomatic MBC patients, "tumor shrinkage . . . is directly correlated with a decrease in tumor pain," even if that is not fully captured in quality of life reporting.[131] These perspectives are echoed in the conclusions of the NCCN breast cancer panel, composed of expert breast cancer clinicians and researchers.

The ODAC's lack of breast cancer expertise also affected the panel's evaluation of Avastin's safety. One member declared, for example, that the higher incidence of hypertension and proteinuria among Avastin patients "would require more doctor visits to control blood pressure, to monitor, et cetera,"[132] leading to "anxiety."[133] Dr. O'Shaughnessy, a breast cancer specialist, addressed this concern, noting that "patients don't have to make any extra trips to the office for hypertension or proteinuria monitoring."[134] Dr. Powderly, another

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[129] Transcript, June 29, 2011 Public Hearing at 86:8-12.

[130] *Id.* at 168:4-8.

[131] Transcript, June 28, 2011 Public Hearing at 59:19-60:9; *see also id.* at 29:2-4 (reporting "a quality of life that is nothing short of miraculous"); Docket No. FDA-2010-N-0621 at Regulations.gov (docket submissions from patients favoring Avastin's continued approval).

[132] Transcript, June 29, 2011 Public Hearing at 240:10-16.

[133] *Id.* at 149:18-21.

[134] *Id.* at 241:11-242:3.

breast cancer specialist, explained that "[o]ncologists are well versed in managing Avastin and its side effects" based upon the medication's use in other indications.[135] One patient with TNBC recounted that her hypertension is asymptomatic and her proteinuria is managed with adjustments in her treatment cycle.[136]

The more serious adverse events associated with Avastin are also manageable with careful clinical judgments within the capabilities of experienced breast cancer clinicians. Dr. O'Shaughnessy noted: "It really boils down to patient selection. . . . [R]eally, really carefully asking people about prior history of diverticulitis, for example. What's their history of arterial vascular disease? Longstanding hypertension; big-time smokers. You really have to weigh those risks and benefits."[137] The ODAC's contrary conclusion ignores the widespread clinical understanding of Avastin's risks by those with clinical experience and underestimates the ability of oncologists who see breast cancer patients in their practices to perform this routine risk-benefit calculus.

As one ODAC member recognized: "I think a lot of this revolves around what efficacy means, and what does it mean to the physicians, and what does it mean to the patients. It cannot be an abstract or statistical concept by itself."[138] Yet the ODAC panelists' lack of insight into Avastin's role in real-world clinical practice, and its apparent unwillingness to take into account the views of MBC patients and breast oncologists, limit the utility of the conclusions reached by the panel.

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[135] Transcript, June 28, 2011 Public Hearing at 60:10-14.

[136] Transcript, June 28, 2011 Public Hearing at 37:3-12.

[137] Transcript, June 29, 2011 Public Hearing at 153:9-154:4.

[138] *Id.* at 216:15-19.

CONCLUSION

Two facts cannot be disputed in the wake of the hearing to withdraw Avastin's breast cancer indication: the approved treatment options for patients with metastatic breast cancer are extremely limited, particularly for patients who face aggressive disease; and Avastin in combination with weekly paclitaxel indisputably has an effect on this form of breast cancer. These facts drive Genentech's proposal to retain accelerated approval for Avastin plus paclitaxel, subject to a confirmatory study and with revised labeling and risk communications that respond directly to the views CDER has expressed regarding Avastin.

On these facts, where there is a middle-ground means of addressing the questions that CDER has raised, it would be contrary to the public health and the goals of the accelerated approval process to withdraw the breast cancer indication.

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.

August 4, 2011

APPENDIX A

Proposed Revisions to the Avastin® (bevacizumab) Package Insert: Metastatic Breast Cancer

August 4, 2011

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

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OVERVIEW AND BACKGROUND

On February 22, 2008, the United States (US) Food and Drug Administration (FDA) granted Avastin (bevacizumab) marketing approval under the accelerated approval of biological products regulations (21 CFR §601.40-46) for use in combination with paclitaxel, for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer based on data from Study E2100. With the accelerated approval, the Avastin® US Package Insert was updated to include data from Studies E2100 (safety and efficacy) and AVF2119g (supportive safety data).

On November 16, 2009, in accordance with the postmarketing study commitment and the reporting requirements of 21 CFR §601.70, Genentech submitted two supplemental Biologics License Applications (sBLAs) with new information regarding the use of Avastin for the treatment of patients with previously untreated (e.g. first-line) metastatic breast cancer (mBC) in combination with standard cytotoxic chemotherapies based on data from the following studies:

- Study BO17708 (AVADO): randomized, multicenter, placebo-controlled Phase III study, which evaluated Avastin in combination with docetaxel for previously untreated, locally recurrent or metastatic HER2-negative breast cancer.
- Study AVF3694g (RIBBON1): randomized, multicenter, placebo-controlled Phase III study, which evaluated Avastin in combination with taxane-based chemotherapy (docetaxel or Abraxane®), anthracycline-based therapy or capecitabine for previously untreated, locally recurrent or metastatic HER2-negative breast cancer. This study consisted of two independently powered cohorts under a single protocol: the taxane- or anthracyline-based chemotherapy cohort and the capecitabine cohort.

On July 16, 2010, Genentech also submitted an sBLA with new information based on data from Study AVF3693g (RIBBON2). RIBBON2 was a Phase III multicenter, randomized placebo-controlled trial, which evaluated the efficacy and safety of Avastin in combination with chemotherapy regimens (taxanes, gemcitabine, capecitabine and vinorelbine) in subjects with previously treated (e.g. second-line) mBC.

On December 16, 2010, the Center for Drug Evaluation and Research (CDER) issued Complete Response letters for the three sBLAs based on AVADO, RIBBON1 and RIBBON2, stating that the data did not demonstrate sufficient benefit to outweigh the risks. Additionally, due to CDER's determination that the subsequent studies, AVADO and RIBBON1, along with RIBBON2, did not confirm the magnitude of benefit from E2100, CDER communicated

that it was proposing to withdraw marketing approval of the drug in breast cancer and issued a Notice of Opportunity for a Hearing. Genentech requested the hearing and the Commissioner of Food and Drugs (M. Hamburg) granted the hearing, conducted in accordance with procedures set forth in 21 CFR Part 15 and 21 CFR §601.43 on June 28-29, 2011.

In documentation and testimony prior to and during the hearing, Genentech has consistently communicated the company's willingness to collaborate with FDA to "find a solution, such as a modified or restricted label"[1] in order to retain accelerated approval while a confirmatory study is conducted to verify clinical benefit for Avastin + paclitaxel in mBC. Therefore, Genentech is proposing a modified label in accordance with its middle-ground proposal based on the science and the best interest of patients.

The purpose of this document is to describe the rationale supporting proposed revisions to the Full Prescribing Information (FPI) that are proposed for consideration by Commissioner Hamburg to maintain accelerated approval for Avastin, in combination with weekly paclitaxel, for the treatment of patients who have not received chemotherapy for their HER2-negative metastatic breast cancer.

The specific sections of the draft label that have been revised and are described in this document are: Highlights, Indication and Usage, Warnings and Precautions, Adverse Reactions, and Clinical Studies.

HIGHLIGHTS

The Highlights section has been updated as per 21 CFR §201.57(a) and FDA's labeling guidance[2] with relevant changes regarding mBC to the following sections of the Highlights: Recent Major Changes, Indications and Usage, and Adverse Reactions. These changes are consistent with the proposed revisions to the Full Prescribing Information, and the detailed rationale for these revisions is provided in the sections below.

[1] Transcript, June 29, 2011 Public Hearing at 104:20-21.
[2] FDA Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (January 2006)

FULL PRESCRIBING INFORMATION (FPI)

INDICATION AND USAGE (3)

The proposed revision to the indication is outlined below in the underlined text:

> *Avastin is indicated in combination with weekly paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and who have disease characteristics (e.g. aggressive HR+/HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment.*
>
> *The effectiveness of Avastin in mBC is based on an improvement in progression free survival in a single study. Two additional studies with different chemotherapy combinations did not confirm the same magnitude of benefit. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. Physicians and patients should consider whether the benefit is sufficient to offset the risks described in the Warnings and Precautions [See Warnings and Precautions (5) and Clinical Studies (14.3).]*
>
> *Avastin is not indicated 1) in combination with other chemotherapies for patients who have not received chemotherapy for mBC, or 2) for patients who have received prior chemotherapy for mBC.*

In accordance with 21 CFR §201.57(c)(2)(i)(e), (c)(2)(ii), (c)(2)(iv)[3] regarding specific requirements on content and format of labeling for human prescription drugs, Genentech proposes to retain the indication for Avastin in combination with paclitaxel based on the efficacy and safety from Study E2100. Genentech is proposing to adopt modified labeling to limit Avastin's approved use to those areas where the unmet medical need is most acute[4], requiring the use of combination therapy as assessed by the treating oncologist. Examples of these patients include those with tumors who have aggressive hormone receptor (HR) positive disease with unfavorable characteristics (e.g. visceral disease, high tumor burden and rapid disease progression) or those with triple-negative mBC.[5] Patients with these

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[3] 21 CFR §201.57(c)(2)(i)(e) states "*If safety considerations are such that the drug should be reserved for specific situations, e.g. cases refractory to other drugs, this information shall be stated in this section*."; 21 CFR §201.57(c)(2)(ii) states *"If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product generally do not outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective for that use or condition."*

[4] Post-hearing Submission of Genentech, Inc. (Docket No. FDA-2010-N-0621), Section I.

[5] Patients with triple-negative mBC (TNBC) have tumors that do not express hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]) and do not overexpress HER2. They are commonly referred to as TNBC or HR-/HER2-. Also refer to Appendix C, Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease.

disease characteristics are examples of subgroups that have a poor prognosis and critically limited treatment options[6]. Therefore, Genentech believes it is appropriate to retain Avastin with paclitaxel as an approved treatment within this context of deep unmet medical need and limited treatment alternatives.

Genentech acknowledges that choice of treatment for a patient is influenced by many factors, including disease characteristics, presence or absence of symptoms, prior treatment in the adjuvant setting, safety and tolerability considerations, and personal choice. As such, it is important that the physician and patient assess whether other treatment options may be more appropriate and whether the benefits outweigh the risks of treatment with Avastin + paclitaxel. The aim of the proposed language "*and who have disease characteristics (e.g. aggressive HR+/HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment"* and "*Physicians and patients should consider whether this benefit is sufficient to offset the risks described in the Warnings and Precautions [See Warnings and Precautions (5) and Clinical Studies (14.3).]*" is to ensure that these principles are clear and emphasized in the labeling.

In accordance with 21 CFR §201.56(a)(1), 201.57(c)(2)(i)(B)[7] and FDA's labeling guidance[8] Genentech proposes to describe the basis of effectiveness data for Avastin + paclitaxel in mBC based solely on a single study, E2100, and set out that two subsequent studies (AVADO and RIBBON1) did not confirm the same magnitude of benefit. Additionally, the proposed language clearly identifies that there are no data demonstrating an improvement in disease-related symptoms or increased survival in all three Avastin studies in the first-line setting.

All five Avastin mBC Phase III studies (E2100, AVADO, RIBBON1, RIBBON2, AVF2119g) were adequate and well-controlled studies, as per 21 CFR §314.126. Consistent with FDA's

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[6] Appendix C, Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease.

[7] 21 CFR §201.56(a)(1) states "*The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.";* 21 CFR §201.57(c)(2)(i)(B) states *"If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under 314.510 or 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section for a discussion of the available evidence."*

[8] FDA Final Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drug and Biological Products – Content and Format (January 2006)

labeling guidance[9] which states: "*The CLINICAL STUDIES section of labeling must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively (21 CFR 201.57(c)(15))*", the proposal includes the totality of evidence of Avastin in mBC, including information from studies AVADO, RIBBON1 and RIBBON2, in addition to the information for E2100 and AVF2119g which is currently included in the US Package Insert). Genentech proposes to revise the language in the indication statement to make clear that Avastin is not indicated "*1) in combination with other chemotherapies for patients who have not received chemotherapy for mBC, or 2) for patients who have received prior chemotherapy for mBC"*, and in order to limit any confusion regarding approved chemotherapy combinations in this patient population.

Overall, the proposed language for the indication statement is factual, based on the scientific data, in response to the review comments raised by CDER, and is in accordance with 21 CFR §201.56(a)(2)[10].

WARNINGS AND PRECAUTIONS (5)

The Warnings and Precautions section consists of general information important to the understanding of Avastin use across indications, in accordance with the requirements of 21 CFR 201.57(c)(6) and FDA's labeling guidance.[11] The safety data from AVADO, RIBBON1 and RIBBON2 demonstrated a safety profile that is consistent with the events described for mBC patients treated with Avastin (based on E2100 and AVF2119g) in the Package Insert as well as what is expected across the approved indications. Data from all five Avastin mBC studies were analyzed and assessed against incidence rates and ranges already reported in the subsections of Warnings and Precautions. Several subsections of Warnings and Precautions did not require an update as the incidence rates observed in the additional studies were consistent with the information reported in the currently approved FPI, namely "Surgery and Wound Healing Complications", "Hemorrhage", "Non-Gastrointestinal Fistula

[9] FDA Final Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drug and Biological Products – Content and Format (January 2006); pg 2 "*Clinical studies that provide other important information about a drug's effectiveness not furnished by the studies that provide primary support for effectiveness such as:…Studies that suggest lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where the drug might have been expected to work…Studies that provide information about the nature and size of the treatment effect, particularly where the effect is small."*

[10] 21 CFR §201.56(a)(2) states *"The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular."*

[11] FDA Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (January 2006)

Formation", "Reversible Posterior Leukoencephalopathy Syndrome", "Proteinuria" and "Infusion Reactions".

There are three subsections in which the overall incidence rates of the adverse reactions in the Warnings and Precautions subsections have been updated based on the Avastin mBC studies; however, these changes are minor and do not alter the overall safety profile of Avastin across all indications. The changes are indicated in underlined text below:

- Section 5.1 Warnings and Precautions (Gastrointestinal Perforations) was revised with updated incidence rate to reflect a change in the lower bound range from 0.3% to 0.5% among controlled clinical trials across indications: "*The incidence of gastrointestinal perforation ranged from 0.5 to 2.4% across clinical studies.*"
- Section 5.5 Warnings and Precautions (Arterial Thromboembolic Events) was revised with updated incidence in the following statement: "*Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.0% compared to 0.8% in the control arms*."
- Section 5.6 Warnings and Precautions (Hypertension) was revised with updated incidence rate in the following statement: "*Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 4.5-18%*".

ADVERSE REACTIONS (6)

The Adverse Reactions section was revised to include information from Studies AVADO, RIBBON1, and RIBBON2 in addition to the existing information from E2100 and AVF2119g, in accordance with 21 CFR §201.56(a)(1), 201.57(c)(7)[12] and FDA's labeling guidance.[13]

In Section 6 Adverse Reactions, the description of the most common adverse reactions observed in Avastin patients across clinical trials was determined using the same criteria that has been applied across the other approved indications: >10% incidence rate and at least twice the rate observed in the control arm in studies that collected all grades of adverse events. In Study AVADO, the terms "*conjunctivitis", "dysphonia",* and *"weight loss*" were the adverse reactions that met these criteria and were therefore added to the listing of the most common adverse reactions observed in Avastin patients across clinical trials, resulting in changes outlined in underlined text below:

[12] 21 CFR §201.57(c)(7) states "*This section must describe the overall adverse reaction profile of the drug based on the entire safety database."*

[13] FDA Final Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (January 2006)

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

Additionally, the following statement was updated to reflect rate of Avastin discontinuation due to adverse reactions across the studies to include the mBC data:

"Across all studies, Avastin was discontinued in 8.4 to 25.1% of patients because of adverse reactions."

Section 6.1 Clinical Trial Experience

In Section 6.1 Clinical Trial Experience, the description of the data sources has been updated to include the data from Studies AVADO, RIBBON1 and RIBBON2 to supplement the existing information based on E2100 and AVF2119g. Consistent with the approach across indications in the approved labeling, the data sources are based on patients treated with Avastin from these studies, and all changes are noted as underlined text:

"The data below reflect exposure to Avastin in 4183 patients with mCRC, non-squamous NSCLC, mBC, glioblastoma, or mRCC primarily in controlled (Studies 1, 2, 4, 5, 6, 7, 8, 9 and 12) or uncontrolled, single arm (Study 10) trials treated at the recommended dose and schedule for a median of 8 to 16 doses of Avastin. [See Clinical Studies (14).] The population was aged 21-91 years (median 58), 29.4% male and 73.8% white. The population included 1089 first- and second-line mCRC patients who received a median of 11 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 2114 mBC patients (the majority of whom had not previously received chemotherapy for their metastatic disease) who received a median of 10 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin."

Additional language has been added to specific Clinical Trials Experience (Section 6.1) to reflect data for patients treated with Avastin plus various chemotherapy regimens, as outlined as underlined text:

- **Proteinuria subsection:** The mBC studies demonstrated that the incidence rates of Grade 3-4 proteinuria are within the range of incidence across indications in the current approved Avastin Package Insert (0.7 to 7.4% incidence of Grade 3-4 proteinuria across indications). The detailed information about proteinuria in this section is from Study 12 in renal cell carcinoma (RCC) patients, in which all but two of the 649 patients enrolled had prior full or partial nephrectomy, resulting in a

higher incidence of proteinuria.[14] As the nature of the disease in RCC does not directly apply to patients with mBC, the Proteinuria subsection was revised to ensure clarity regarding the information sourced from Study 12.

- **Congestive Heart Failure (CHF) subsection:** Based on the body of safety data for Avastin across indications and specifically for patients with mBC, the "*Congestive Heart Failure*" subsection was revised to better reflect the risk of patients with mBC in contrast to the patients with other types of cancer. The analyses demonstrated that patients with cancers other than mBC have a similar risk for experiencing a CHF-related event between the Avastin-containing arm and the control arm. Regarding patients with previously untreated mBC, the data demonstrate that there is a higher risk of experiencing a Grade ≥3 CHF event when treated with Avastin in combination with chemotherapy, and that this incidence is further elevated if the mBC patient was previously treated with an anthracycline-based chemotherapy in the adjuvant setting. Therefore, the language specific to mBC has been updated with incidence rates and accurate language to reflect the inclusion of data from Studies AVADO and RIBBON1:

  > *"The incidence of Grade ≥ 3 left ventricular dysfunction was 0.5% in patients receiving Avastin compared to 0.6% in the control arm across indications, other than mBC. In patients with mBC with no prior adjuvant or concurrent anthracycline use, the incidence of Grade ≥3 congestive heart failure (CHF) was 0.5% in the Avastin plus chemotherapy arm compared to 0.2% in the control arm. Among mBC patients with a history of adjuvant anthracycline use, the rate of Grade ≥3 CHF was 2.0% for patients receiving Avastin as compared to 0.3% for patients receiving chemotherapy alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied."*

Metastatic Breast Cancer (mBC) Subsection

In alignment with the method of denoting clinical trials within the currently approved language in the Avastin Package Insert, the Avastin mBC studies have been reassigned study number references in the draft labeling. The ordering of the studies takes into consideration the setting (previously untreated patients with mBC followed by previously treated mBC patients), as well as the chronology of the study conduct, the study data availability, and subsequent regulatory review. As such, Study E2100 remains "Study 5", AVADO has been denoted as "Study 6", RIBBON1 has been denoted "Study 7", AVF2119g is now denoted as "Study 8", and RIBBON2 is denoted as "Study 9". As a result, the pivotal studies for glioblastoma multiforme (GBM) and renal cell carcinoma (RCC) have now been

[14] Post-hearing Submission of Genentech, Inc. (Docket No. FDA-2010-N-0621), Section IIIb

renamed Studies 10 and 11, and 12, respectively. For your reference, please refer to Attachment A for a comprehensive study legend for the studies described in the revised Avastin® Package Insert, and referred to in this rationale document.

Consistent with 21 CFR §201.57 (c)(7) and the FDA's labeling guidance[15], the "*Metastatic Breast Cancer (mBC)*" subsection of Section 6 - Adverse Reactions (Clinical Trials Experience) has been updated to describe the totality of data that represent the safety experience for Avastin in mBC based on data from Studies E2100, AVADO, RIBBON1, AVF2119g and RIBBON2. In an effort to ensure that the safety data across these studies are presented in a manner that makes it easier for health care practitioners to identify the adverse reactions information that is most important to prescribing decisions, the following factors were taken into consideration in presenting the data in this subsection:

1. The safety data from E2100 already in the current labeling has been retained. While Genentech views the data as supporting a favorable benefit-risk balance for Avastin plus paclitaxel for the overall population of patients who have not received chemotherapy for HER2-negative mBC, this balance is especially compelling for poor prognosis patients such as those with triple-negative mBC or aggressive course of HR+/HER2- disease, who have limited treatment options and are faced with a more acute medical need. Exploratory subgroup analyses on this important subgroup has been performed and are discussed,[16] and Genentech proposes to include a descriptive statement regarding the safety experience of these patients within the subsection describing safety from E2100:

   "The safety experience of patients in the subgroup HR-/HER2- subgroup was consistent with the overall safety population."

2. Provision of clarity on the studies that are presented in this subsection and why this information is important to physicians and patients:

   "Avastin is not approved for use in combination with other chemotherapies for first-line treatment of mBC (Studies 6, 7), or in second-line (Study 9) or second- or third-line treatment of mBC (Study 8). Studies 6 and 8 collected all adverse events and the data below are presented to supplement information on the overall safety profile of Avastin in women with breast cancer."

   The proposed wording clearly states that there are no approved claims based on AVADO (Study 6), RIBBON1 (Study 7), AVF2119g (Study 8) or RIBBON2 (Study 9).

[15] FDA Final Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (January 2006)
[16] Appendix C, Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease.

Study E2100 collected only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events, while studies AVADO and AVF2119g collected all grades of adverse events in the entire study population. Therefore, the language described above includes the safety information from AVADO and AVF2119g, which supplement the safety data from Study E2100. Genentech proposes to describe the Grade 1-5 adverse events that occurred ≥5% in the Avastin-containing arm compared to the control arm from AVADO and retain the existing safety information describing Grade 1-4 adverse events occurring at ≥5% between treatment arms from AVF2119g in narrative listing form (previously presented in tabular format in the current labeling for Avastin).

CLINICAL STUDIES (14)

Based on the rationale discussed above for the other sections of the FPI, and in accordance with 21 CFR §201.56(a)(2), §201.57 (c)(15), and FDA's labeling guidance,[17] Section 14.3 "Metastatic Breast Cancer" in Clinical Studies has been revised to describe the totality of data regarding the effectiveness and safety for Avastin in mBC based on data from all five studies. Specifically, the inclusion of data from all five studies (inclusion of AVADO, RIBBON1, and RIBBON2 to supplement the existing information for E2100 and AVF2119g) adheres to the guidance that all studies were adequate and well-controlled, and that *"The CLINICAL STUDIES section of labeling must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively."* [18]

The proposal for language in the Clinical Studies section for mBC (14.3) ensures that the efficacy data across these studies are clearly outlined for patients and health care practitioners to inform treatment decisions. The language proposed is also consistent with the information provided across the approved indications for Avastin and informed by FDA's labeling guidance. Please note the following regarding the organization of the information:

1. As discussed in previous sections, Genentech proposes to include information regarding studies AVADO, RIBBON1 and RIBBON2 to supplement the information already included in the label for E2100 and AVF2119g. This information would be limited to a brief description of the study design, patient population, key outcome measures, and limitations of the data (see points 3-5 below).

[17] FDA Final Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (January 2006)
[18] *Id.* and 21 CFR §314.126

2. The studies are grouped in chronological order within similar patient populations, presenting the first-line mBC studies (E2100 as Study 5, AVADO as Study 6, RIBBON1 as Study 7), followed by AVF2119g (which enrolled primarily second- and third-line patients) and finally, RIBBON2 (second-line mBC).

3. The existing language describing the critical design aspects, population studied, endpoints measured and important limitations of the available evidence regarding E2100 are retained. Consistent with the rationale and approach described in the Adverse Reactions subsection for mBC, Genentech proposes to include a descriptive statement at the end of the language describing secondary endpoints from E2100 regarding the exploratory subgroup analyses on the important subgroup of triple negative mBC, which has been performed and are discussed within the post-hearing submission as an example of a subgroup with poor prognosis and heightened unmet medical need:[19]

   "Exploratory analyses were conducted in poor prognosis subgroups of mBC (e.g. patients with HR-/HER2- tumors). The PFS magnitude in these subgroups was consistent with the overall population."

4. The information for AVADO (Study 6) and RIBBON1 (Study 7) are presented together as they were conducted in similar populations of patients who had not previously received chemotherapy for metastatic disease and had the same primary outcome measure of investigator-assessed progression free survival. Following a brief description of the study design and control chemotherapy, a factual statement is also included regarding the outcome of both studies, consistent with CDER's review of the data:

   "Both studies demonstrated statistically significant PFS improvement, of lesser magnitude than Study 5, and did not demonstrate an improvement in OS."

   Genentech proposes to include the primary data for progression free survival for both AVADO and RIBBON1 in textual narrative format and in a factual manner. As outlined in FDA's labeling guidance[20], the proposed data are appropriate to include, clearly defining the magnitude of PFS outcome (expressed in both median PFS and hazard ratio) to be lesser than observed in E2100 (Study 5).

5. The previous language for AVF2119g has been retained under "Study 8". An important distinction among the mBC studies is that 23% of the patients enrolled in AVF2119g were HER2+, in contrast to the other four studies that enrolled primarily HER2- patients.

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[19] Appendix C, Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease.

[20] FDA Final Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (January 2006) states "*…the amount of detail needed to provide a useful description of a study and its results will depend on the indication, the trial design, the understanding of the drug or drug class, and the extent to which the information adds to an understanding of the clinical effects of the drug and how the drug should be used"; "Ordinarily, applicants should include more detail when…The study uses an unfamiliar endpoint (e.g., a novel surrogate endpoint), or there are important limitations and uncertainties associated with an endpoint."; "The CLINICAL STUDIES section should present those endpoints that establish the effectiveness of the drug or show the limitations of effectiveness."*

As such, minor addition to the description of patient population to include the language in underlined text:

"Of the 462 enrolled patients, the median age was 51 years, 81% were white, 50% were ER-positive, and 23% were HER2-positive."

6. Information for RIBBON2 is provided under "Study 9". Similar to the language for AVADO and RIBBON1, the language for RIBBON2 includes a brief description of the study design, patient population, and primary results for PFS. Additionally, a factual statement that reflects CDER's view of the data is included:

   "The statistically significant PFS improvement was lesser than the magnitude observed in Study 5 and no improvement in overall survival was observed at the interim analysis."

CONCLUSION

The modified labeling presented here for Avastin in the mBC indication is consistent with Genentech's proposed middle-ground approach, which preserves access for the patients with the greatest unmet medical need. Retaining approval with this revised labeling is the correct outcome for patients and the public health based on the science and the purposes of accelerated approval. The language proposed is consistent with the principles and guidelines outlined in the regulations and FDA's labeling guidance.

Genentech's proposed labeling seeks to respond to the points CDER has raised by restricting Avastin's approved use to those areas where the unmet medical need is most acute, such as aggressive hormone receptor positive mBC or triple-negative mBC. The unique medical need for patients with especially poor prognoses animates the benefit-risk determination under accelerated approval and supports retaining the treatment option that Avastin represents for these patients.

Attachment A
Avastin Full Prescribing Information Study Legend

Study Number	United States Package Insert (Version December 2010)	Label Proposal (July 2011)
1	AVF2107g (mCRC)	AVF2107g
2	E3200 (mCRC)	E3200
3	TRC-0301 (mCRC)	TRC-0301
4	E4599 (NSCLC)	E4599
5	E2100 (mBC)	E32100
6	AVF2119g (mBC)	BO17708 (AVADO; mBC)
7	AVF3708g (GBM)	AVF3694g (RIBBON1; mBC)
8	NCI-FINE (GBM)	AVF2119g (mBC)
9	BO17708 (AVOREN; RCC)	AVF3693g (RIBBON2; mBC)
10	—	AVF3708g
11	—	NCI-FINE
12	—	BO17708 (AVOREN)

GBM = glioblastoma multiforme; mBC = metastatic breast cancer; mCRC = metastatic colorectal cancer; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma

Attachment B
Draft Red-Lined Changes to Avastin® United States Package Insert

ATTACHMENT B - DRAFT RED-LINED LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

See full prescribing information for complete boxed warning.

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

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

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

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

- Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment. (1.1)
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)
- Metastatic breast cancer, with weekly paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and who have disease characteristics (e.g. aggressive HR+/HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment. (1.3)
  -Effectiveness based on improvement in progression-free survival in one study. Two additional studies with other chemotherapy partners did not confirm the same magnitude of benefit No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
  -Not indicated ~~for~~ 1) in combination with other chemotherapies for patients with HER2-negative metastatic disease who 1) have not received chemotherapy for mBC, or 2) ~~disease progression following~~ for patients who have received prior chemotherapy for mBC ~~anthracycline and taxane chemotherapy administered for metastatic disease.~~
- Glioblastoma, as a single agent for patients with progressive disease following prior therapy. (1.4)
  -Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
- Metastatic renal cell carcinoma with interferon alfa (1.5)

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

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

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

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

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

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

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

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

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

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

None (4)

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

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

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: ~~December 2010~~XXXX 20XX

ATTACHMENT B - DRAFT RED-LINED LABELING

FULL PRESCRIBING INFORMATION: CONTENTS*

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

ATTACHMENT B - DRAFT RED-LINED LABELING

FULL PRESCRIBING INFORMATION

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

Gastrointestinal Perforations

The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.5~~3~~ to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. ***[See Dosage and Administration (2.4), Warnings and Precautions (5.1).]***

Surgery and Wound Healing Complications

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

Hemorrhage

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

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

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

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

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

1.3 Metastatic Breast Cancer (m~~M~~BC)

Avastin is indicated in combination with weekly paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer ~~in combination with paclitaxel~~and who have disease characteristics (e.g. aggressive HR+/ HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment.

The effectiveness of Avastin in m~~M~~BC is based on an improvement in progression free survival in a single study. Two additional studies with different chemotherapy combinations in the same setting did not confirm the same magnitude of benefit. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. Physicians and patients should consider whether the benefit is sufficient to offset the risks described in the Warnings and Precautions *[See Warnings and Precautions (5) and Clinical Studies (14.3).]*

Avastin is not indicated ~~for patients~~ 1) in combination with other chemotherapies for patients who have not received chemotherapy for mBC, or 2) for patients who have received prior chemotherapy for mBC ~~with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease~~.

1.4 Glioblastoma

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

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

1.5 Metastatic Renal Cell Carcinoma (mRCC)

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

2 DOSAGE AND ADMINISTRATION

2.1 Administration

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

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

2.2 Recommended Doses and Schedules

Patients should continue treatment until disease progression or unacceptable toxicity.

Metastatic Colorectal Cancer (mCRC)

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

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

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

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

Metastatic Breast Cancer (~~M~~mBC)

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

Glioblastoma

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

Metastatic Renal Cell Carcinoma (mRCC)

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

2.3 Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

2.4 Dose Modifications

There are no recommended dose reductions.

Discontinue Avastin for:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ *[See Boxed Warning, Warnings and Precautions (5.1, 5.4).]*
- Wound dehiscence and wound healing complications requiring medical intervention *[See Warnings and Precautions (5.2).]*

- Serious hemorrhage (i.e., requiring medical intervention) *[See Boxed Warning, Warnings and Precautions (5.3).]*
- Severe arterial thromboembolic events *[See Warnings and Precautions (5.5).]*
- Hypertensive crisis or hypertensive encephalopathy *[See Warnings and Precautions (5.6).]*
- Reversible posterior leukoencephalopathy syndrome (RPLS) *[See Warnings and Precautions (5.7).]*
- Nephrotic syndrome *[See Warnings and Precautions (5.8).]*

Temporarily suspend Avastin for:

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.5~~3~~ to 2.4% across clinical studies. *[See Adverse Reactions (6.1).]*

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

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

5.2 Surgery and Wound Healing Complications

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

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

The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days. Suspend Avastin for at least 28 days prior to elective surgery. Do not administer Avastin until the wound is fully healed. *[See Boxed Warning, Dosage and Administration (2.4).]*

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal

hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. *[See Adverse Reactions (6.1).]*

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

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

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

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

5.4 Non-Gastrointestinal Fistula Formation

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

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

5.5 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was ~~2.4~~2.0% compared to 0.8~~7~~% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years. *[See Use in Specific Populations (8.5).]*

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

5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 4.5-18%.

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

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

5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been reported with an incidence of <0.1% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of Avastin. RPLS is a neurological disorder which

can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of RPLS.

Discontinue Avastin in patients developing RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing RPLS is not known. *[See Dosage and Administration (2.4).]*

5.8 Proteinuria

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

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

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

5.9 Infusion Reactions

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

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

6 ADVERSE REACTIONS

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

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

The most common adverse reactions observed in Avastin patients at a rate > 10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration,

conjunctivitis, dry skin, rectal hemorrhage, lacrimation disorder, back pain, ~~and~~ exfoliative dermatitis, dysphonia and weight loss.

Across all studies, Avastin was discontinued in 8.4 to 25.1% of patients because of adverse reactions.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Avastin in ~~2661~~ 4183 patients with mCRC, non-squamous NSCLC, m~~M~~BC, glioblastoma, or mRCC primarily in controlled (Studies 1, 2, 4, 5, 6, 7, 8, 9 and 12~~9~~) or uncontrolled, single arm (Study 10~~7~~) trials treated at the recommended dose and schedule for a median of 8 to 16 doses of Avastin. *[See Clinical Studies (14).]* The population was aged 21-91~~88~~ years (median 5~~89~~), ~~46.0~~29.4% male and ~~84.1~~73.8% white. The population included 1089 first- and second-line mCRC patients who received a median of 11 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, ~~592~~ 2114 ~~M~~mBC patients (the majority of whom had not previously received chemotherapy for their metastatic disease) who received a median of 10~~8~~ doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin.

Surgery and Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving Avastin as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus Avastin as compared to 4% (1/25) of patients who received bolus-IFL alone.

In Study 10~~7~~, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).]*

Hemorrhage

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus Avastin compared with patients receiving bolus-IFL plus placebo. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).]*

Venous Thromboembolic Events

The incidence of Grade 3–4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone. The risk of developing a second subsequent thromboembolic event in mCRC patients receiving Avastin and chemotherapy was increased compared to patients receiving chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following Grade 3–4 venous thromboembolic events was higher in

patients receiving bolus-IFL plus Avastin as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

Neutropenia and Infection

The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs. 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

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

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4, 5, 6, 7, 8, 9 and 12~~9~~. The overall incidence of proteinuria (all grades) was ~~only adequately~~further assessed in patients with renal cell carcinoma (Study 12)~~9~~, in which the incidence was 20%. In Study 12, m~~M~~edian onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 12~~9~~). *[See Warnings and Precautions (5.8).]*

Congestive Heart Failure

The incidence of Grade ≥ 3 left ventricular dysfunction was ~~1.~~0.5% in patients receiving Avastin compared to 0.6% in the control arm across indications other than mBC. In patients with m~~M~~BC with no prior adjuvant or concurrant anthracycline use, the incidence of Grade ≥ 3~~-4~~ congestive heart failure (CHF) was ~~increased~~ 0.5% ~~in patients~~ in the Avastin plus paclitaxel arm ~~(2.2%) as~~ compared to 0.2% in the control arm ~~(0.3%)~~. Among mBC patients with a history of adjuvant ~~receiving prior~~ anthracycline use~~s for MBC~~, the rate of Grade ≥ 3 CHF was ~~3.8~~2.0% for patients receiving Avastin as compared to 0.~~6~~3% for patients receiving ~~paclitaxel~~ chemotherapy alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

Metastatic Colorectal Cancer (mCRC)

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

All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Severe and life-threatening (Grade 3–4) adverse events, which occurred at a higher incidence (≥ 2%) in patients receiving bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.

Table 1
NCI-CTC Grade 3–4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥ 2%] Avastin vs. Control)

	Arm 1 IFL + Placebo (n = 396)	Arm 2 IFL + Avastin (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
Leukopenia	31%	37%
Neutropenia[a]	14%	21%

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

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

Table 2
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥5%] in IFL+Avastin vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+Avastin (n=102)	Arm 3 5-FU/LV+Avastin (n=109)
Body as a Whole			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%

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Table 2 (cont'd)
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥5%] in IFL+Avastin vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+Avastin (n=102)	Arm 3 5-FU/LV +Avastin (n=109)
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

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

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

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

Metastatic Breast Cancer (mMBC)

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

Sensory neuropathy, hypertension, and fatigue were reported at a ≥ 5% higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm. The safety experience of patients in the HR-/HER2- subgroup was consistent with the overall safety population.

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

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

~~Table 3~~

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

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

Avastin is not approved for use in combination with other chemotherapies for first-line treatment of mBC (Studies 6, 7), or in second-line (Study 9) or second- or third- line treatment of mBC (Study 8). Studies 6 and 8 collected all adverse events and the data below are presented to supplement information on the overall safety profile of Avastin in women with breast cancer.

In Study 6, Grade 1-5 adverse events occurring at a higher incidence (≥ 5%) in 247 patients receiving docetaxel plus Avastin compared to the 231 patients receiving docetaxel plus placebo were: epistaxis (49% vs. 20%), lacrimation increased (47% vs. 27%), stomatitis (44% vs. 26%), arthralgia (33% vs. 20%), anorexia (32% vs. 24%), mucosal inflammation (29% vs. 23%), headache (28% vs. 22%), hypertension (22% vs. 10%), febrile neutropenia (18% vs. 12%), dyspersia (17% vs. 11%), conjunctivitis (15% vs. 6%), palmar-plantar erythrodysaesthesia syndrome (15% vs. 9%),

dysphonia (11% vs. 3%), weight decreased (10% vs. 4%), onycholysis (9% vs. 4%), and proteinuria (7% vs. 2%).

In Study 8, Grade 1-4 adverse events occurring at a higher incidence (≥ 5%) in 229 patients receiving capecitabine plus Avastin compared to the 215 patients receiving capecitabine alone were: exfoliative dermatitis (84% vs. 75%), asthenia (57% vs. 47%), headache (33% vs. 13%), pain (31% vs. 25%), dyspnea (27% vs. 18%), stomatitis (25% vs. 19%), hypertension (24% vs. 2%), albuminuria (22% vs. 7%), epistaxis (16% vs. 1%), myalgia (14% vs. 8%), and weight loss (9% vs. 4%).

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 107 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

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

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

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 129. Grade 3–5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving interferon alfa (IFN-α) plus Avastin compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

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

Table 4

NCI-CTC Grades 1–5 Adverse Events in Study 129 (Occuring at Higher Incidence [≥ 5%] in IFN-α + Avastin vs. IFN-α + Placebo)

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

*Adverse events were encoded using MedDRA, Version 10.1.

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

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and

underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

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

Body as a Whole: Polyserositis
Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion
Eye disorders (reported from unapproved use for treatment of various ocular disorders): Endophthalmitis; Intraocular inflammation such as iritis and vitritis; Retinal detachment; Other retinal disorders; Increased intraocular pressure; Hemorrhage following intraocular injection including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Visual disturbances; Ocular hyperemia; Ocular pain and/or discomfort
Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation, dysphonia

7 DRUG INTERACTIONS

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

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

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

8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of

the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the half-life of the bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the mother. *[See Clinical Pharmacology (12.3).]*

8.4 Pediatric Use

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

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

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥ 2%) in patients aged ≥65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged≥ 65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 4, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. *[See Warnings and Precautions (5.8).]*

In Studies~~y~~ 5-9, there were insufficient numbers of patients ≥ 65 years old in each study to determine whether the overall adverse events profile was different in the elderly as compared with younger patients.

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged≥65 years and 1127 patients<65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged≥65 years (8.5% vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). *[See Warnings and Precautions (5.5).]*

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

11 DESCRIPTION

Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Avastin has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of Avastin (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

12.3 Pharmacokinetics

The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of bevacizumab every 2 weeks was 2.8.

The clearance of bevacizumab varied by body weight, gender, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger V_c (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. In Study 1, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin as compared to females and patients with low tumor burden. The relationship between bevacizumab exposure and clinical outcomes has not been explored.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies of bevacizumab have been conducted.

Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

13.2 Animal Toxicology and/or Pharmacology

In cynomolgus monkeys, when bevacizumab was administered at doses of 0.4 to 20 times the weekly human exposure, anatomical pathology revealed several adverse effects on general growth

and skeletal development, fertility and wound healing capacity. Severe physeal dysplasia was consistently reported in juvenile monkeys with open growth plates receiving 0.4 to 20 times the human dose. The physeal dysplasia was characterized by a linear cessation of growth line and chondrocyte hyperplasia which did not completely resolve after the 4 to 12 weeks recovery period without drug exposure.

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

13.3 Reproductive and Developmental Toxicology

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

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer (mCRC)

Study 1

In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL (irinotecan 125 mg/m^2, 5-FU 500 mg/m^2, and leucovorin (LV) 20 mg/m^2 given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

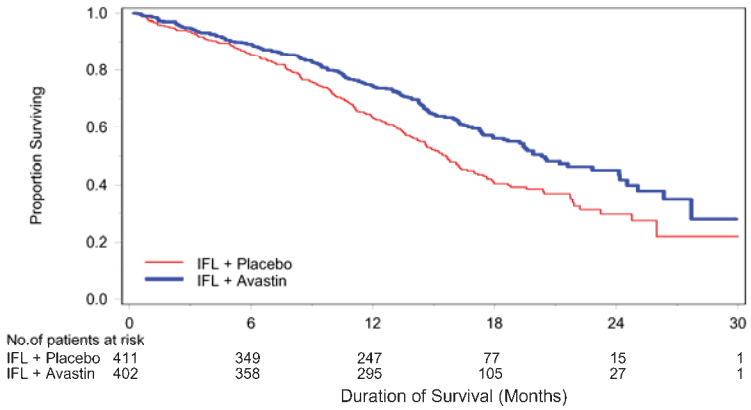
The addition of Avastin resulted in an improvement in survival across subgroups defined by age (< 65 yrs, ≥ 65 yrs) and gender. Results are presented in Table 5 and Figure 1.

Table 5
Study 1 Efficacy Results

	IFL + Placebo	IFL + Avastin 5 mg/kg q 2 wks
Number of Patients	411	402
Overall Survival[a]		
Median (months)	15.6	20.3
Hazard ratio		0.66
Progression-free Survival[a]		
Median (months)	6.2	10.6
Hazard ratio		0.54
Overall Response Rate[b]		
Rate (percent)	35%	45%
Duration of Response		
Median (months)	7.1	10.4

[a] $p < 0.001$ by stratified log rank test.
[b] $p < 0.01$ by χ^2 test.

Figure 1
Duration of Survival in Study 1



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

Study 2

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

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

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

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

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

Study 3

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

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

Study 4

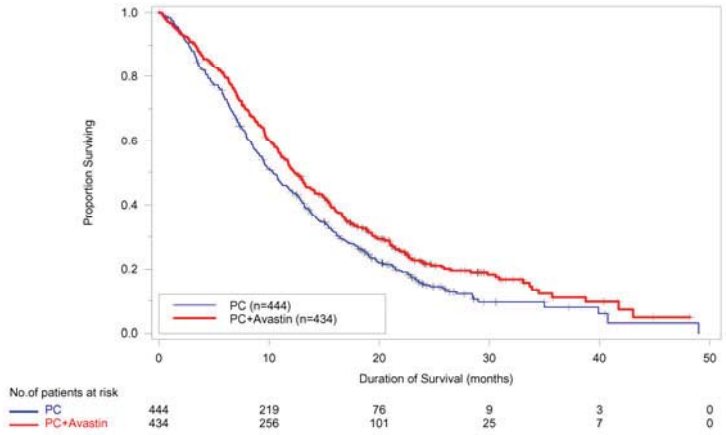
The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study.

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

Of the 878 patients randomized, the median age was 63, 46% were female, 43% were $\geq$ age 65, and 28% had $\geq$ 5% weight loss at study entry. Eleven percent had recurrent disease and of the 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

The results are presented in Figure 2. OS was statistically significantly higher among patients receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs. 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank test]. Based on investigator assessment which was not independently verified, patients were reported to have longer PFS with Avastin in combination with PC compared to PC alone.

Figure 2
Duration of Survival in Study 4



In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust in the following: women [HR = 0.99 (95% CI: 0.79, 1.25)], age ≥ 65 years [HR = 0.91 (95% CI: 0.72, 1.14)] and patients with ≥5% weight loss at study entry [HR = 0.96 (95% CI: 0.73, 1.26)].

14.3 Metastatic Breast Cancer (~~M~~mBC)

Study 5

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

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

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

Table 6
Avastin Efficacy Results from Study 5

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

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

The addition of Avastin to paclitaxel resulted in an improvement in PFS with no significant improvement in OS. Partial response rates in patients with measurable disease were higher with Avastin plus paclitaxel. No complete responses were observed. Exploratory analyses were conducted in poor prognosis subgroups of mBC (e.g. patients with HR-/HER2- tumors). The PFS magnitude in these subgroups was consistent with the overall population.

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

Study 6 & 7

The efficacy and safety of Avastin as first-line treatment of patients with HER2-negative mBC was studied in two additional randomized, placebo-controlled, multicenter studies in combination with docetaxel (Study 6, n=736) or other chemotherapies (Study 7, n=622 in Cohort 1 with taxanes or anthracyclines, and n=615 in Cohort 2 with capecitabine). Patients who had not received chemotherapy for locally recurrent or metastatic HER2-negative breast cancer were enrolled. The main outcome measure of both studies with PFS by investigator assessment. Both studies demonstrated statistically significant PFS improvement, of lesser magnitude than Study 5, and did not demonstrate an improvement in OS.

In Study 6, the median PFS was 7.9 months in the docetaxel plus placebo arm and 8.8 months in the docetaxel plus Avastin arm (hazard ratio 0.62, p-value=0.0003). In Study 7, patients were randomized into two cohorts, with patients receiving taxane or anthracycline plus placebo or Avastin (Cohort 1), and patients receiving capecitabine plus placebo or Avastin (Cohort 2). The median PFS in the control arm was 8.0 months and 9.2 months in the Avastin-containing arm in Cohort 1 (hazard ratio 0.64, p<0.0001), while in Cohort 2, the median PFS in the control arm was 5.7 months and 8.6 months in the Avastin-containing arm (hazard ratio 0.69, p=0.0002).

Study 8

The efficacy and safety of Avastin as second- and third-line treatment of patients with ~~M~~mBC was studied in a single open-label randomized study. Patients who had received prior anthracycline and taxane therapy in the adjuvant setting or for their m~~M~~BC were randomized (1:1) to receive capecitabine alone or in combination with Avastin. Of the 462 enrolled patients, the median age was 51 years, 81% were white, ~~and~~ 50% were ER positive, and 23% were HER2-positive. Patient characteristics were similar across the treatment arms.

The study failed to demonstrate a statistically significant effect on PFS or OS. The median PFS was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm

(log-rank p-value = 0.86, hazard ratio 0.98). The median OS was 14.5 months in the capecitabine arm and 15.1 months in the capecitabine plus Avastin arm (hazard ratio of 1.08).

Study 9

The efficacy and safety of Avastin as second-line treatment of patients with HER2-negative mBC in combination with various chemotherapies (taxanes, capecitabine, gemcitabine, vinorelbine) was studied in a single randomized, placebo-controlled multicenter study. Patients who had received prior chemotherapy in the first-line setting were enrolled (n=684). The main outcome measure was PFS pooled across all chemotherapy cohorts as assessed by the investigator. The median PFS was 5.1 months in the chemotherapy plus placebo arm and 7.2 months in the chemotherapy plus Avastin arm (hazard ratio 0.78, p=0.0072). The statistically significant PFS improvement was lesser than the magnitude observed in Study 5 and no improvement in overall survival was observed at the interim analysis.

14.4 Glioblastoma

Study 107

The efficacy and safety of Avastin was evaluated in Study 107, an open-label, multicenter, randomized, non-comparative study of patients with previously treated glioblastoma. Patients received Avastin (10 mg/kg IV) alone or Avastin plus irinotecan every 2 weeks until disease progression or until unacceptable toxicity. All patients received prior radiotherapy (completed at least 8 weeks prior to receiving Avastin) and temozolomide. Patients with active brain hemorrhage were excluded.

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

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

Study 118

Study 118, was a single-arm, single institution trial with 56 patients with glioblastoma. All patients had documented disease progression after receiving temozolomide and radiation therapy. Patients received Avastin 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

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

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

14.5 Metastatic Renal Cell Carcinoma (mRCC)

Study 129

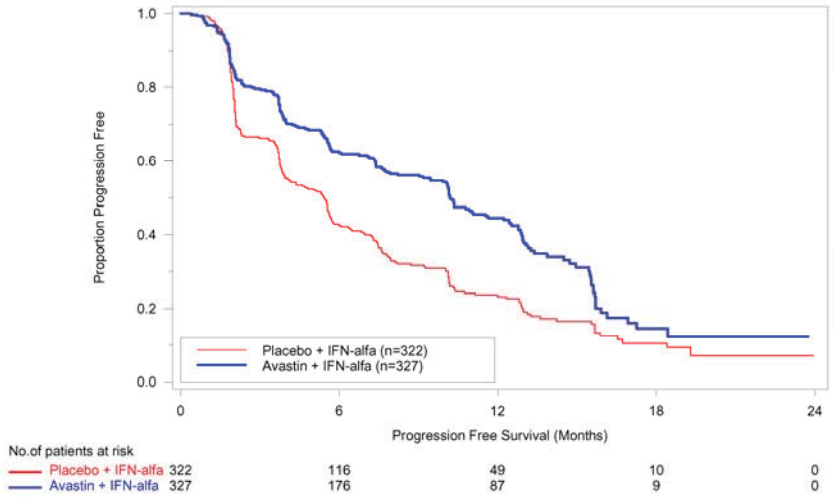
Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind, international study comparing Avastin plus interferon alfa 2a (IFN- α2a) versus placebo plus IFN-α2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10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

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

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

Figure 3

Progression-Free Survival in Study 129



16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

17 PATIENT COUNSELING INFORMATION

Advise patients:

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

Avastin® (bevacizumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

~~10127309~~XXXXXXXX
Initial U.S.Approval: February 2004
Code Revision Date: ~~December~~ XXXX 201~~0~~X
Avastin® is a registered trademark of Genentech, Inc.

APPENDIX B

AVASTIN® (bevacizumab)

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

A. To encourage informed benefit-risk decisions regarding the use of Avastin in combination with paclitaxel in individual patients with metastatic breast cancer (mBC).

B. To inform healthcare professionals (HCPs) that the benefit of Avastin in mBC is limited to an improvement in progression-free survival (PFS) when used in combination with paclitaxel; the magnitude of PFS effect for Avastin with different chemotherapy agents has ranged from hazard ratios of 0.61 to 0.48 and the median PFS effect has ranged from 0.9 months to 5.5 months; and that there are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.

C. To inform HCPs and patients about the increase in risk for the serious adverse events **gastrointestinal perforations, surgery and wound healing complications, and hemorrhage** as well as non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), proteinuria, and infusion reactions associated with Avastin.

D. To inform HCPs and patients that the indication for Avastin in combination with weekly paclitaxel for mBC is limited to the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and who have disease characteristics (e.g. aggressive HR+/HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment.

II. AVASTIN REMS ELEMENTS

The proposed REMS includes the following components:

- **Medication Guide:** Provided to patients with Avastin mBC prescription
- **Communication Plan:** Targeted to HCPs who prescribe and administer Avastin for mBC.
- **Assessments:** To determine whether the Medication Guide and Communication Plan are meeting the goals of the Avastin REMS program.

The Medication Guide enables communication of the Avastin benefit-risk profile to mBC patients and the Communication Plan ensures all prescribers are knowledgeable about the benefit-risk profile of Avastin for mBC. Each component of the proposed REMS contributes to ensuring the safe and effective use of Avastin in combination with paclitaxel in the treatment of mBC.

A. Medication Guide

In accordance with 21 CFR 208.24, Genentech will ensure the Avastin Medication Guide is distributed with each package for HCPs to dispense to each patient who is administered Avastin. Every Avastin package will include the U.S. Prescribing Information and Medication Guide.

The carton package will include a prominent instruction to dispensers to provide a Medication Guide to each patient to whom the drug is administered.

B. Communication Plan

Genentech will implement a Communication Plan to HCPs who prescribe and administer Avastin to support implementation of the REMS. The Communication Plan consists of a Dear Healthcare Professional (DHCP) Letter and Avastin mBC Healthcare Professional Training Guide to help educate HCPs on the key educational messages to communicate to patients when discussing the benefit-risk profile of Avastin in mBC.

1. DHCP Letter

The DHCP Letter will be distributed to oncologists listed in the American Medical Association (AMA) list, any physician who has prescribed Avastin over the last two years, and associated infusion centers where Avastin has been prescribed and administered.

Genentech will send the DHCP Letter electronically to providers for whom email addresses are available. Genentech will purchase available email addresses from the AMA. Targeted providers whose email addresses are not available from the AMA will receive the DHCP Letter through U.S. mail. Additionally, the sales representatives will make the DHCP Letter available to HCPs upon approval of the REMS. The DHCP Letter will also be available through a REMS-dedicated link from the www.avastin.com website.

In addition, Genentech will distribute the DHCP Letter to the following professional societies: American Society of Clinical Oncology and other breast cancer associations [TBD]. Genentech will request that these societies provide the letter to their membership. Following initial distribution, pending any updates to the professional label, Medication Guide or training materials, an updated DHCP Letter will be sent to these professional societies with a request that they provide the letter to their membership.

The DHCP Letter will convey important information to providers on the indication for Avastin in mBC and on the benefits and risks associated with the use of Avastin in mBC, to encourage fully informed benefit-risk decisions, including that Avastin plus paclitaxel is approved for use in mBC based on an improvement in PFS in a single study. Two additional studies with different chemotherapy combinations in the same setting did not confirm the same magnitude of benefit. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. The DHCP Letter will also communicate that the use of Avastin in mBC is associated with serious risks including the risks of **gastrointestinal perforations, surgery**

and wound healing complications, hemorrhage, non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, RPLS, proteinuria, and infusion reactions.

The mailing will also include the following materials:

- A copy of the Prescribing Information and the Medication Guide, and the Avastin mBC Healthcare Professional Training Guide.

These materials will also be available upon request through the Genentech toll-free medical information line, and through a REMS-dedicated link from the www.avastin.com website.

2. REMS Program Website

The REMS Program Website for HCPs will be accessed through a REMS-dedicated link directly from the Avastin.com homepage. Included in the information will be an explanation of the REMS, the goal of the REMS for Avastin in mBC, and separate links for downloadable versions of the full Prescribing Information, the Medication Guide, the DHCP Letter, and the Avastin mBC Healthcare Professional Training Guide. The REMS Webpage will also include the indication for Avastin in mBC, information for HCPs about the benefit-risk profile of Avastin in combination with paclitaxel for mBC, and a link for patients and caregivers to return to the Avastin homepage.

The online information will be available to all HCPs as it is in the public domain.

The following materials are part of the REMS and are attached:

- Medication Guide (Appendix 1)
- Dear Healthcare Professional Letter (Appendix 2)
- Avastin mBC Healthcare Professional Training Guide (Appendix 3)

C. Elements to Assure Safe Use

Elements to Assure Safe Use are not required.

D. Implementation System

An Implementation System is not required.

E. Timetable for Submission of Assessments

Genentech will submit REMS Assessments to FDA at 18 months, 3 years and 7 years after approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Genentech will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix 1

MEDICATION GUIDE
Avastin® (a-VASS-tin) for Breast Cancer
(Generic name: bevacizumab)

Read the Medication Guide given to you before you start Avastin for your breast cancer and each time you get a new prescription. The information may have changed. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Talk with your doctor if you have any questions about your treatment with Avastin.

What is the most important information I should know about Avastin?

Avastin can cause serious side effects that can lead to death, including:

- **Gastrointestinal (GI) perforation.** GI perforation is the development of a hole in the stomach, small intestine, or large intestine. Symptoms may include stomach pain, nausea, vomiting, constipation, and fever. Your Avastin therapy should be stopped if GI perforation occurs.
- **Slow or incomplete wound healing.** This can happen when a cut from surgery has trouble healing or staying closed. Your doctor should not start you on Avastin for at least 28 days after surgery and until the cut from surgery is fully healed. Your doctor should stop Avastin for at least 28 days before any surgery you may choose to have. Your Avastin therapy should be stopped if you have slow or incomplete wound healing.
- **Bleeding.** This can happen if you cough up blood, have bleeding in your stomach, vomit blood, have bleeding in your brain, have nosebleeds, or bleed from your vagina. If you have recently coughed up blood or have other serious bleeding problems you should not receive Avastin.

You should speak with your doctor about the incidence of these potentially serious side effects and weigh these risks against the benefits of Avastin for your breast cancer.

The benefit of taking Avastin for your breast cancer is based on one clinical study of Avastin combined with paclitaxel where improvement in progression-free survival (the time patients lived without their tumors growing or spreading) was measured. The study showed that patients taking Avastin with paclitaxel had a 52% reduction in the risk of disease progression or death compared to patients taking paclitaxel alone. The median (middle) time patients lived without their tumors growing or spreading was 11.3 months for Avastin with paclitaxel and 5.5 months with paclitaxel alone. Two other studies where Avastin was combined with different chemotherapies did not show the same benefit. In these studies, patients taking Avastin plus chemotherapy had a 31% to 38% reduction in the risk of disease progression or death compared to chemotherapy alone. The median (middle) times patients lived without their tumors growing or spreading ranged from 0.9 to 2.9 months longer for those who received Avastin plus chemotherapy compared to chemotherapy alone.

In all three studies, there are no data showing an improvement in symptoms related to breast cancer or survival.

What is Avastin?

- Avastin, is a tumor-starving (anti-angiogenic) therapy. It is used with the chemotherapy medicine paclitaxel (Taxol®) to treat HER2-negative metastatic breast cancer (mBC) in people who have not yet received chemotherapy for metastatic disease, whose breast cancer is likely to have a poor outcome (e.g. aggressive HR+/HER2- or HR-/HER2- tumors) and for whom treatment with other options is not thought to be appropriate by their doctor.
    - Metastatic breast cancer is when the cancer has spread to a new part of the body, but the new tumors are made up of cells from the original breast tumor.
    - HER2 is a type of protein that can help determine what kind of breast cancer you have. You should only consider Avastin plus paclitaxel if you have HER2-negative breast cancer.
    - HER2-negative breast cancer may be either hormone receptor-positive, or HR+ (has a protein on the cell surface that binds to the hormones estrogen or progesterone), or hormone receptor-negative, or HR-.
- Avastin is not approved for people who have taken anthracycline and taxane chemotherapy in the past for their HER2-negative mBC.
- Avastin is also approved to treat 3 other common cancers: lung, colon, and kidney.

How should I take Avastin?

- You take Avastin as an infusion. That means you receive Avastin through a small needle in your vein or through a port.
- The recommended dose is 10 mg/kg every 2 weeks in combination with paclitaxel.

What should I avoid while taking Avastin?

Avastin therapy is not right for everyone with HER2-negative mBC. You cannot start Avastin if you have finished a taxane-based therapy, such as Taxol® or Taxotere®, for early-stage breast cancer, in the last 12 months.

Talk to your doctor if you:

- Are pregnant, think you may be pregnant, or are planning to become pregnant. Based on animal data, Avastin may harm the fetus.
- Are breast-feeding. Avastin may pass into your breast milk.

Tell your doctor about all your medical conditions and all the medicines you take including prescription, nonprescription, and herbal medicines. Avastin and other medicines may affect each other, causing side effects. Do not start any new medicines until you check with your doctor.

What are the possible side effects of Avastin?

Avastin can cause serious and life-threatening side effects (See "What is the most important information I should know about Avastin?"), including:

- The formation of an abnormal passage from parts of the body to another part.
- Stroke or heart problems. Heart problems include blood clots, mini-stroke, heart attack, and chest pain.
- Too much protein in the urine
- High blood pressure.
- Nervous system and vision problems. Symptoms may include high blood pressure, headache, seizure, sluggishness, confusion, and blindness.
- Infusion reactions. These may include high blood pressure or severe high blood pressure that may lead to stroke, a hard time breathing, low oxygen in red blood cells, a serious allergic reaction, chest pain, headaches, tremors, and a lot of sweating.

The most common side effects of Avastin include:

- Nosebleeds
- Headache
- High blood pressure
- Swelling of the nose
- Too much protein in the urine
- Taste change
- Dry skin
- Rectal bleeding
- Tear production disorder
- Back pain
- Swelling of the skin

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see enclosed full Product Information, including Serious Side Effects, for additional important safety information.

General Information about Avastin

This Medication Guide provides a summary of the most important information about Avastin. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information or have any questions, talk with your doctor. You can ask your doctor for information about Avastin that is written for healthcare professionals. You can also visit www.avastin.com or call 1-877-4AVASTIN.

What are the ingredients in Avastin?

Active: Bevacizumab (humanized anti-VEGF monoclonal antibody)
Inactive: Trehalose dihydrate
Sodium phosphate
Polysorbate 20
Water for injection

Marketed by:
Manufactured by:

Genentech, Inc.

A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Revised 08/2011

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Appendix 2

Dear Healthcare Professional Letter

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional,

The purpose of this letter is to inform you about important efficacy and safety information for Avastin® (bevacizumab) in the treatment of metastatic breast cancer (mBC).

Genentech, with agreement from the U.S. Food and Drug Administration (FDA), developed the Avastin Risk Evaluation and Mitigation Strategy (REMS) Program to provide information to support an informed decision for each patient as to whether the benefits of Avastin in mBC outweigh the risks.

mBC Indication

Avastin is indicated in combination with weekly paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and who have disease characteristics (e.g. aggressive HR+/HER2- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment.

Avastin is not indicated 1) in combination with other chemotherapies for patients who have not received chemotherapy for mBC, or 2) for patients who have received prior chemotherapy for mBC.

Important Efficacy Information

The effectiveness of Avastin in mBC is based on an improvement in progression-free survival (PFS) in a single study of Avastin in combination with paclitaxel. PFS is the time before disease progression as measured by tumor growth. The study demonstrated a 5.5 month improvement in median PFS and a 52% reduction in the risk of disease progression or death. Two additional studies with different chemotherapy combinations in the same setting did not confirm the same magnitude of benefit. Avastin in combination with different chemotherapies demonstrated improvements in median PFS of 0.9 month to 2.9 months, and a 31 – 38% reduction in the risk of disease progression or death. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin in all three studies.

Physicians and patients should consider whether the benefits is sufficient to offset the serious risks associated with Avastin use and whether there are other more appropriate treatment options.

Boxed WARNINGS and Additional Important Safety Information

- **Gastrointestinal (GI) perforation:** Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls. The incidences of GI perforation ranged from 0.5% to 2.4% across clinical studies. Discontinue Avastin in patients with GI perforation.
- **Surgery and wound healing complications:** The incidence of wound healing and

surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound dehiscence requiring medical intervention.

- **Hemorrhage:** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood). Discontinue Avastin in patients with serious hemorrhage (i.e., requiring medical intervention).
- Additional serious and sometimes fatal adverse events for which the incidence was increased in the Avastin-treated arm vs. control included non-GI fistula formation (≤0.3%), arterial thromboembolic events (grade ≥3, 1.9%), and proteinuria including nephrotic syndrome (<1%). Additional serious adverse events for which the incidence was increased in the Avastin-treated arm vs. control included hypertension (grade 3–4, 4.5%–18%) and reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%). Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients.
- The most common adverse reactions observed in Avastin patients at a rate > 10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, conjunctivitis, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis, dysphonia and weight loss. Across all studies, Avastin was discontinued in 8.4 to 25.1% of patients because of adverse reactions.
- Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin. Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal, and pain/weakness/hypotension (2).

Physicians and patients should carefully consider whether the benefits of Avastin in mBC are sufficient to offset the significant risks associated with Avastin use as described in the Warnings and Precautions section of the Prescribing Information and other prescribing information for an individual patient.

The Avastin REMS Program

The goals of the REMS Program are to ensure that healthcare professionals and their patients:

- Understand the benefits associated with Avastin treatment in mBC
- Understand the risks associated with Avastin treatment in mBC
- Understand the limitations on the indication for Avastin treatment in mBC.

Your role in the REMS Program

As a healthcare professional, your responsibilities in the REMS Program are to:

- Read the Medication Guide, full Prescribing Information, and the Avastin REMS Program educational material
- Provide mBC patients with a Medication Guide
- Educate patients about the benefits and risks associated with Avastin in mBC
- Report any pregnancies and adverse events to Genentech Drug Safety, and encourage patients to share information about a pregnancy and/or adverse event with Genentech Drug Safety.

REPORTING ADVERSE EVENTS

It is important that you report all adverse events, including any pregnancies that occur in patients who take Avastin for mBC. **Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. HIPPA does not apply to this adverse event reporting.

You can report adverse events to Genentech Drug Safety or directly to the FDA:

- Genentech Drug Safety at 1-XXX-XXX-XXXX
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

This letter is not a comprehensive description of the benefits and risks associated with the use of Avastin. Please read the accompanying full Prescribing Information and Medication Guide for a complete description of these benefits and risks. The Medication Guide contains information that can be used to facilitate discussion with your patients about the risks of therapy.

To obtain additional copies of the Avastin Medication Guide:

- Print copies from www.avastin.com
- Call the Avastin REMS Program Call Center at 1-XXX-XXX-XXXX to request that copies be mailed to you.

For more information, please visit www.avastin.com or call the Avastin REMS Program Call Center at 1-XXX-XXX-XXXX.

Please see enclosed full Prescribing Information and Medication Guide.

Sincerely,

Hal Barron, MD
Chief Medical Officer, USA
Genentech, Inc.
Enclosures

Appendix 3

Avastin mBC Healthcare Professional Training Guide

The Avastin® (bevacizumab) Risk Evaluation and Mitigation Strategy Program

The Avastin REMS Program is designed to provide information and support to healthcare professionals (HCPs) and patients concerning the safe and appropriate use of Avastin for metastatic breast cancer (mBC). The REMS Program is what the U.S. Food and Drug Administration (FDA) refers to as a Risk Evaluation and Mitigation Strategy (REMS), implemented as part of the FDA Amendments Act of 2007.

mBC Indication

Avastin is indicated in combination with weekly paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and who have disease characteristics (e.g. aggressive HR+/HER- or HR-/HER2- tumors) for which other therapies are considered to be less appropriate per physician assessment.

Avastin is not indicated 1) in combination with other chemotherapies for patients who have not received chemotherapy for mBC, or 2) for patients who have received prior chemotherapy.

Important Efficacy Information

The effectiveness of Avastin in mBC is based on an improvement in progression-free survival (PFS) in a single study of Avastin in combination with paclitaxel. PFS is the time before disease progression as measured by tumor growth. The study demonstrated a 5.5 month improvement in median PFS and a 52% reduction in the risk of disease progression or death. Two additional studies with different chemotherapy combinations in the same setting did not confirm the same magnitude of benefit. Avastin in combination with different chemotherapies demonstrated improvements in median PFS of 0.9 month to 2.9 months, and a 31-38% reduction in the risk of disease progression or death. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin in all three studies.

Physicians and patients should consider whether the benefit is sufficient to offset the serious risks associated with Avastin use and whether there are other more appropriate treatment options.

Important Safety Information

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

Use of Avastin has been associated with an identified risk of **gastrointestinal perforations, surgery and wound healing complications, hemorrhage**, non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), proteinuria, and infusion reactions associated with Avastin.

The goals of the REMS Program are to:

- To encourage informed benefit-risk decisions regarding the use of Avastin in combination with paclitaxel in individual patients with metastatic breast cancer (mBC).
- To inform healthcare professionals (HCPs) that the benefit of Avastin in mBC is limited to an improvement in progression-free survival (PFS) when used in combination with paclitaxel, the magnitude of median PFS effect for Avastin with different chemotherapy agents has ranged from hazard ratios of 0.61 to 0.48 and the median PFS effect has ranged from 0.9 months to 5.5 months, and that there are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.
- To inform HCPs and patients about the increase in risk for the serious adverse events **gastrointestinal perforations, surgery and wound healing complications, hemorrhage**, as well as non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), proteinuria, and infusion reactions associated with Avastin.
- To inform HCPs and patients that the indication for Avastin in combination with weekly paclitaxel for mBC is limited to the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer and who have disease characteristics (e.g. aggressive HR+ or ER-/PR-/HER2- tumors) for which other therapies are considered to be less appropriate by their physician.

In addition, Genentech will collect information about adverse events and pregnancies in patients taking Avastin for mBC.

Your role in the REMS Program is to:

As a healthcare professional, your responsibilities in the REMS Program are to:

- Read the Medication Guide, Prescribing Information, and the Avastin REMS educational material
- Provide mBC patients with a Medication Guide
- Educate patients about the benefit-risk profile of Avastin in mBC
- Report any pregnancies and adverse events to Genentech Drug Safety, and encourage patients to share information about an adverse event and/or pregnancy with Genentech Drug Safety.

Reporting an Adverse Event

If a patient has an adverse event or becomes pregnant during mBC therapy, you should:

- Report the adverse event or pregnancy to Genentech Drug Safety at 1-XXX-XXX-XXXX.
- Genentech Drug Safety will contact you and the patient to collect data to characterize the risks associated with Avastin.

Avastin Dosage and Administration

Administration

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

Recommended Doses and Schedules

- Patients should continue treatment until disease progression or unacceptable toxicity.
- The recommended dose for mBC is 10 mg/kg every 2 weeks in combination with paclitaxel.

Boxed WARNINGS and Additional Important Safety Information

- **Gastrointestinal (GI) perforation:** Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls. The incidences of GI perforation ranged from 0.5% to 2.4% across clinical studies. Discontinue Avastin in patients with GI perforation.
- **Surgery and wound healing complications:** The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound dehiscence requiring medical intervention.
- **Hemorrhage:** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood). Discontinue Avastin in patients with serious hemorrhage (i.e., requiring medical intervention).
- Additional serious and sometimes fatal adverse events for which the incidence was increased in the Avastin-treated arm vs. control included non-GI fistula formation (≤0.3%), arterial thromboembolic events (grade ≥3, 1.9%), and proteinuria including nephrotic syndrome (<1%). Additional serious adverse events for which the incidence was increased in the Avastin-treated arm vs. control included hypertension (grade 3–4,

4.5%–18%) and reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%). Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients.

- The most common adverse reactions observed in Avastin patients at a rate > 10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, conjunctivitis, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis, dysphonia and weight loss. Across all studies, Avastin was discontinued in 8.4 to 25.1% of patients because of adverse reactions.

Physicians and patients should carefully consider whether the benefits of Avastin in mBC are sufficient to offset the significant risks associated with Avastin use as described in the Warnings and Precautions section of the Prescribing Information and other prescribing information for an individual patient.

For more information:

- About Avastin, visit www.avastin.com.
- About the Avastin REMS Program, visit www.avastin.com or call 1-XXX-XXX-XXXX.

To report an adverse event or pregnancy:

- Genentech Drug Safety 1-XXX-XXX-XXXX.

Please see accompanying full Prescribing Information, including BOXED WARNINGS, Medication Guide, and pages X-X of this booklet for additional Important Safety Information.

APPENDIX C

Discussion Paper: HER2-Negative Metastatic Breast Cancer – A Clinically Heterogeneous Disease

August 03, 2011

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Introduction

From a clinical perspective, HER2-negative metastatic breast cancer may be subdivided into three main groups that help guide management decisions:

1. Indolent hormone receptor (HR)-positive (estrogen receptor positive [ER] and/or progesterone receptor [PR] positive) tumors; best treated with hormonal agents, and sequential single agent chemotherapy when hormone-unresponsive;
2. Aggressive HR-positive tumors, which are often associated with debilitating bone pain, or threaten organ function;
3. ER-/PR-/HER2- (triple negative[1]) tumors, likewise commonly symptomatic and often requiring active and timely intervention.

The latter two entities frequently require combination therapy, in an effort to gain rapid disease control.

When oncologists use their clinical acumen to recognize and appropriately treat metastatic breast cancer that is behaving in an aggressive manner, they are led by a number of clinical disease characteristics that predict a poorer prognosis, regardless of hormone receptor status. These include visceral disease, overall tumor burden (number of metastatic sites and disease extent), short disease-free interval, and tempo of disease progression among other factors. All correlate with poor outcome and generally merit early intervention with highly active regimens, including combination therapies. As discussed above, certain tumor subtypes are more likely to present with one or more of these clinical characteristics. One such subtype is triple negative breast cancer (TNBC).

TNBC: An Example of Aggressive mBC

Up to 24% of patients with invasive breast cancer have tumors classified as TNBC.[2] TNBC has a unique epidemiology: it is 2-3 times more common in African Americans

[1] Also referred to as HR-/HER2- tumors

[2] Bauer KR, Brown M, Cress RD, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Regisry. Cancer 2007, 109(9):1721-1728; Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology and End Results database. Cancer 2007, 110(4):876-884; Carey LA. Directed therapy of subtypes of triple-negative breast cancer. The

(where it represents up to 47% of all breast cancer) and is more common in younger women.[3] The natural history of the disease is distinct, in that it exhibits an aggressive clinical course, with an early pattern of relapse, and a relatively poor prognosis. The location of recurrence is also distinct: patients with this aggressive subtype are more likely to recur with distant metastases, including lung, visceral, and central nervous system metastases.[4]

Women with newly diagnosed metastatic cancer or those with recurrent disease have an especially poor prognosis. In contemporary studies, median life expectancy is 12-16 months for this group.[5]

For the majority of women with metastatic TNBC, medical management requires a focus on disease palliation (preserving a patient's overall functioning and performance status by decreasing or preventing tumor related symptoms) and disease stabilization (prolonging the time that a women lives without her cancer getting worse or dying from the cancer). In clinical practice, therefore, physicians choose the most effective treatments to achieve the best initial response rates and the longest possible progression-free survival, balanced with the least possible treatment-related toxicity.

Chemotherapy has been the mainstay of systemic treatment for TNBC, as endocrine therapy and HER2-directed therapies are ineffective for this population.

Oncologist 2011, 16 Suppl:71-78; Foulkes WD, Smith IE & Reis-Filho JS. Triple-negative breast cancer. N Engl J Med 2010, 363(20):1938-1948.

[3] Additionally, mammographic detection of TNBC can be difficult, and it is more likely than other types of breast cancer to be node-negative. Foulkes WD, Smith IE & Reis-Filho JS. Triple-negative breast cancer. N Engl J Med 2010, 363(20):1938-1948.

[4] Historically, the rate of CNS metastasis in mBC has ranged from 10-16%. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed [1973-2001] in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004, 22(14):2865-2872; Tsukada Y, Fouad A, Pickren JW & Lane WW. Central nervous system metastasis from breast carcinoma: autopsy study. Cancer 1983, 52(12):2349-2354. In a retrospective analysis conducted by Lin *et al* with patients with metastatic TNBC, 46% experienced metastasis to the CNS at any point in the course of disease. Lin NU, Claus E, Sohl J et al. Sites of distant recurrance and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. Cancer 2008, 113(10):2638-2645.

[5] Kassam F, Enright K, Dent R, et al. Survival outcomes for patients with metastatic triple negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer. 2009;9:29-33.

Generally, the choice of chemotherapy agent for TNBC patients is similar to those for non-TNBC patients, and it is accepted that anthracyclines and taxanes are active in this subgroup.[6]

Given the high risk of relapse, patients with early triple-negative disease tend to be treated more aggressively in the adjuvant setting than patients with other breast cancer subtypes. In one registry study, breast cancer patients with small tumors (>0.5 cm to ≤1 cm) were more likely to receive aggressive adjuvant chemotherapy if triple-negative.[7] Consequently, the majority of patients presenting with early TNBC will receive adjuvant or neoadjuvant therapy, limiting the available therapeutic options at time of relapse.

Regardless of the chemotherapy agents used, in the US, combination treatment is commonly administered to achieve rapid control of this biologically aggressive cancer at the time of diagnosis of metastatic disease. The results of E2100 established Avastin plus paclitaxel as a standard of care for patients with HER2-metastatic breast cancer, including those with TNBC. This combination was quickly adopted as an important option because of the favorable efficacy and safety profile relative to other cytotoxic combination therapies that were previously routinely used. As discussed in the sections that follow, the differences in adverse event profiles for treatment options are important considerations for younger TNBC patients who frequently have childcare and other responsibilities.

Experience with Avastin in TNBC

TNBC was analyzed as a subgroup for efficacy in the E2100 study (Table 1). Reflecting the expected poor prognosis for these patients, TNBC patients randomly assigned to the control group and treated with single agent paclitaxel (n=354) had a considerably lower progression free survival (PFS; 5.3 versus 7.4 months) and lower overall survival (OS; 16.3 versus 29.9 months) when compared to non-TNBC patients treated with single agent paclitaxel (n=110 for TNBC patients versus 229 for

[6] Reviewed in Hudis CA & Gianni L. Triple-negative breast cancer: an unmet medical need. The Oncologist 2011, 16 Suppl(1):1-11.

[7] Kaplan HG, Malmgren JA & Atwood M. T1N0 triple negative breast cancer: risk of recurrence and adjuvant chemotherapy. Breast Journal 2009, 15:454-460.

non-TNBC patients). The addition of Avastin to the weekly paclitaxel regimen markedly improved the outcome for these patients, surpassing what would be expected for non-TNBC patients treated with single agent chemotherapy: PFS was 10.6 months versus 5.3 months (HR=0.49, 95%CI 0.34-0.70) and OS was 20.5 months versus 16.3 months (HR=0.89, 95% CI 0.66-1.19) for the Avastin + paclitaxel and paclitaxel groups, respectively. Patients who received Avastin + paclitaxel were more likely to be alive at one year than patients who received single agent chemotherapy (73.8% vs 61.3% or a 12.5% absolute increase). Importantly, overall response rate (ORR) was also higher for patients treated with Avastin + paclitaxel (42.9% vs 21.7%). As seen in Figures 1 and 2, the Kaplan-Meier curves for both PFS and OS in TNBC patients showed an early and sustained separation in favor of patients who received Avastin.

Table 1: Key Efficacy Results by Triple Negative Status in Study E2100

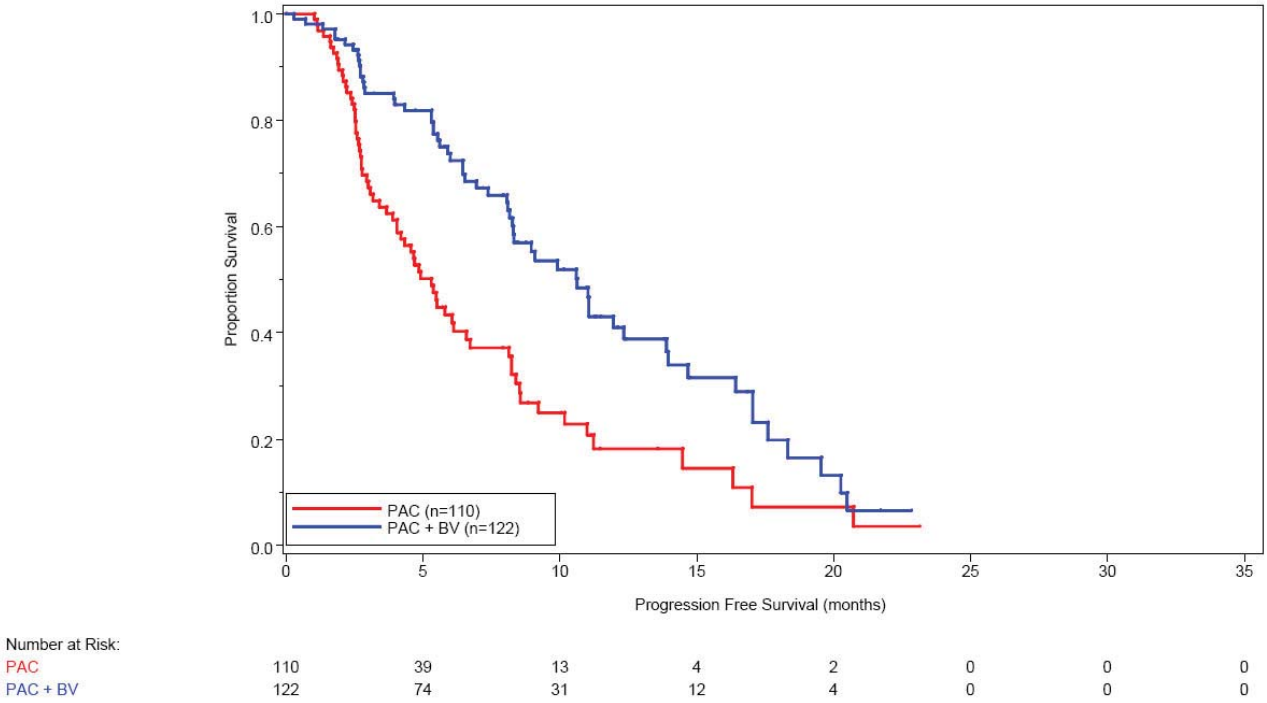
	Avastin + Paclitaxel (n=368)	Paclitaxel (n=354)	Difference	Hazard Ratio (95% CI)
PFS (median, months)*				
TNBC (n= 232)	10.6	5.3	5.3	0.49 (0.34- 0.70)
Non-TNBC (n= 464)	12.1	7.4	4.7	0.56 (0.43 – 0.74)
OS (median, months)*				
TNBC (n= 232)	20.5	16.3	4.2	0.89 (0.66 – 1.19)
Non-TNBC (n= 464)	29.7	29.9	-0.2	0.92 (0.73 – 1.16)
1 Year OS (%)*				
TNBC (n= 232)	73.8	61.3	12.5	12.5 (0.4, 24.5)
Non-TNBC (n=464)	86.3	80.6	5.7	5.7 (-1.1, 12.5)
				Difference (95% CI)
ORR (%)**				
TNBC (n= 167)	42.9	21.7	21.2	21.2 (7.4 – 35.0)
Non-TNBC (n= 290)	53.9	23.5	30.4	30.4 (19.7 – 41.1)

* Unstratified analyses

** For patients with measurable disease only

CI=confidence interval; ORR=overall response rate; OS=overall survival; PFS=progression free survival; TNBC=triple negative breast cancer

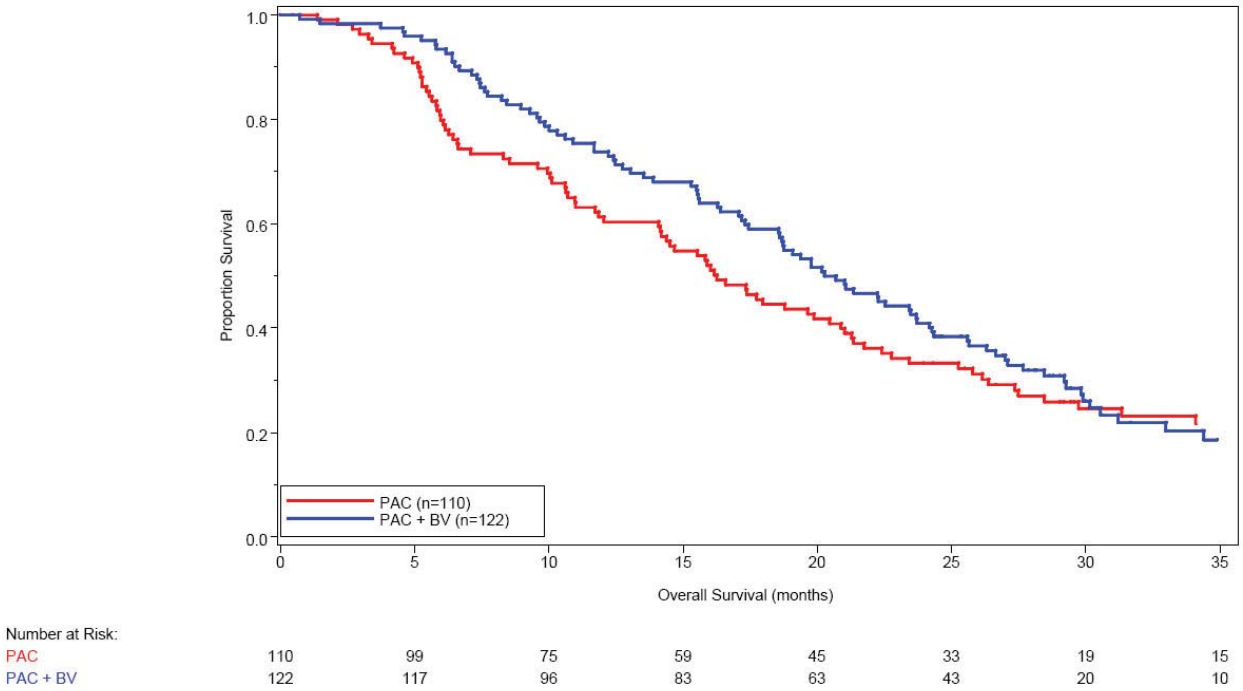
Figure 1: Progression-free Survival Kaplan-Meier Curves for Patients with TNBC Enrolled in E2100



Number at Risk:								
PAC	110	39	13	4	2	0	0	0
PAC + BV	122	74	31	12	4	0	0	0

Bv=Avastin; Pac=paclitaxel; TNBC=triple negative breast cancer

Figure 2: Overall Survival Kaplan-Meier Curves for Patients with TNBC Enrolled in E2100



Bv=Avastin; Pac=paclitaxel; TNBC=triple negative breast cancer

Outcome for the TNBC subgroup from the first-line trials AVADO (BO17708) and RIBBON1 (AVF3694g) are generally in keeping with the broader population. In AVADO, where the chemotherapy backbone was docetaxel, the PFS and OS hazard ratios were 0.53 (95% CI 0.34 - 0.84) and 0.82 (95% CI 0.51 -1.32), respectively, compared to hazard ratios for PFS and OS of 0.67 (95% CI 0.53 - 0.85) and 1.0 (95% CI 0.79 - 1.33), in the broader group.[8]

The overall safety experience in TNBC patients in E2100 is consistent with that described for the overall safety population. Grade 3-5 adverse events occurred in 65.3% of patients on Avastin versus 54.5% in the control arm. The two most commonly observed Grade 3-5 adverse events associated with Avastin

[8] A more detailed presentation of efficacy data in TNBC patients from the Avastin first-line mBC trials was presented in O'Shaughnessy J, Romieu G, et al. Meta-Analysis of Patients with Triple Negative Breast Cancer (TNBC) from Three Randomized Trials of First-Line Bevacizumab (BV) and Chemotherapy Treatment for Metastatic Breast Cancer (MBC). SABCS 2010 Poster Session.

(hypertension and proteinuria) were observed in 4.1% of patients in the Avastin arm (versus 0% in the control arm). In a pooled analysis of the safety population across the first line mBC trials E2100, AVADO and RIBBON1, selected Grade 3-5 adverse events occurred in 34.4% of TNBC patients in the Avastin arm, versus 22.7% in chemotherapy only arms. Similarly Grade 3-5 hypertension and proteinuria was increased to 6.6% from 1.5%.

In E2100, the death rates were comparable between the two treatment arms for the TNBC patients (80.2% versus 80.0% in the experimental and control arms respectively), the vast majority (~77%) being due to disease progression. The deaths due to reasons other than disease progression were 2.5% in the experimental arm compared to 3.6% in the control arm. In the pooled safety population, the death rates (68.3% for the Avastin-containing arm compared to 69.0% in the control arm) are comparable between the two arms for the TNBC patients. The deaths due to reasons other than disease progression were 4.2% in the experimental arm compared to 4.3% in the control arm.

Cytotoxic Chemotherapy For Aggressive Forms of Metastatic BC

Given the aggressiveness of some types of breast cancer in the recurrent or metastatic setting and the subsequent desire to gain rapid disease control, combination therapy is often the treatment of choice. Importantly, due to the lack of expression of ER, PR and the HER2 proteins, endocrine therapy (e.g. tamoxifen and aromatase inhibitors) and HER2-directed therapies (e.g. trastuzumab and lapatinib) are not indicated in the treatment of TNBC at any stage of the disease. Similarly for HR+/HER2- disease progressing after endocrine treatment or those with aggressive (e.g. rapidly growing, symptomatic and/or visceral disease) may require primary treatment with chemotherapy, including combinations of cytotoxic agents.

There are four combinations that are commonly considered as treatment options by US oncologists who routinely care for patients with metastatic breast cancer: Avastin-paclitaxel,[9] gemcitabine-paclitaxel,[10] docetaxel-capecitabine,[11] and

[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; Avastin® United States Package Insert.

ixabepilone-capecitabine.[12] In the modern era, the use of anthracyclines in the metastatic setting (e.g. as part of combinations like CAF[13]) is less common, due to the incorporation of anthracyclines into adjuvant regimens, and the established and widespread use of adjuvant therapy. This is particularly so in the case of TNBC where, despite commonly being node negative, the risk of relapse is high.[14] Of these four combination choices, only Avastin-paclitaxel and gemcitabine-paclitaxel are approved in the US for the first line treatment of HER2- metastatic breast cancer. For the reasons discussed below, Avastin-paclitaxel has been preferentially used by practicing physicians who determine that treatment with more than single agent chemotherapy is indicated to achieve disease control.

During the public hearing for Avastin mBC on June 29, 2011, Dr. Joyce O'Shaughnessy noted during her testimony:

> *"Avastin-paclitaxel provides a higher rate and a longer duration of disease control, as is seen by the improved response rate and the longer progression-free survival in E2100. The magnitude of the PFS and response rate benefit with Avastin-paclitaxel compares favorably to the two to three-month improvement in PFS and the 12- to 15 percent improvement in response rates seen with these approved combination chemotherapy regimens used in clinical practice as first-line treatment."*
>
> *"Importantly, in my experience, Avastin-paclitaxel is a well-tolerated combination regimen. In contrast to combination chemotherapy, the toxicities associated with Avastin-paclitaxel are generally not treatment-limiting."* [15]

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[10] Albain KS, Nag SM, Calderillo-Ruiz G et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol, 2008, 26(24): 3950-3957.

[11] O'Shaugnessy J. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J Clin Oncol 2002, 20(12):2812-2823.

[12] Sparano JA, Vrdoljak E, Rixe O, et al. Randomized Phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2010, 29(20):3256-3263.

[13] Cyclophosphamide, doxorubicin, and fluorouracil.

[14] Kaplan HG, Malmgren JA & Atwood M. T1N0 triple negative breast cancer: risk of recurrence and adjuvant chemotherapy. Breast Journal 2009, 15:454-460.

[15] Transcript, June 29, 2011 Public Hearing at 82:17-83:4, 84:3-7.

Undeniably, considerable toxicities are routinely observed with the chemotherapy combinations. These are often cumulative and treatment limiting and, according to practice guidelines, require frequent monitoring by the physicians.

For instance, as seen in the gemcitabine-paclitaxel study,[16] toxicities were increased in the combination arms, with increased rates of Grade 3/4 neutropenia (47.9%), febrile neutropenia (5%), fatigue (6.9%). Twenty-eight patients in the gemcitabine-paclitaxel combination arm required red cell transfusions, whereas only 10 required such therapy in the single-agent paclitaxel arm.

In general, physicians consider the gemcitabine plus paclitaxel difficult to administer over prolonged treatment periods due to its unfavorable toxicity profile. Indeed, the toxicity profile is easily distinguished from that of Avastin-paclitaxel. In promotional material, gemcitabine-paclitaxel is reported to cause:

- Neutropenia/leucopenia in about 7 out of 10 patients
- Anemia in 69%
- Thrombocytopenia in 26%
- Liver abnormalities requiring the need for regular blood tests prior to each treatment
- Alopecia in 9 out of 10 patients.
- Neuropathy in 64%.
- Tiredness in 4 of 10 patients
- Pain (arthralgia/myalgia) in at least 33% of all patients
- Gastrointestinal upset including nausea and/or vomiting with half of the patients experiencing some degree of nausea, and 3 in 10 patients experiencing some degree of vomiting. Diarrhea is also described in about 1 in 5 patients.

Similarly, notable Grade 3 and 4 adverse events occurred in 31% of patients treated with docetaxel-capecitabine resulting in higher incidences of stomatitis (17.4%),

[16] Albain KS, Nag SM, Calderillo-Ruiz G et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol, 2008, 26(24): 3950-3957.

diarrhea (14.4%), nausea (6%), and hand-foot syndrome (24%), among others.[17] Only 77% of the planned capecitabine dose was delivered and 51% of patients required a dose reduction due to adverse events.

In 2010, Sparano *et al* reported results of a large phase III trial where patients were treated with a novel epothilone B analog, ixabepilone, added to capecitabine in patients previously treated with anthracyclines and a taxane (up to 2 lines of treatment, including neoadjuvant and adjuvant setting).[18] Consistent with the mechanism of action of ixabepilone, sensory neuropathy rates were substantially increased in the experimental arm (24.7%), as well as fatigue (11.8%), Grade 3/4 neutropenia (74%), and febrile neutropenia (7 %).

Practice Patterns in the US

Prior to the July 2010 Oncologic Drugs Advisory Committee (ODAC) for Avastin mBC, breast cancer physicians preferentially used Avastin + paclitaxel for the treatment of HER2 negative breast cancer. However, more recent data on physician practice in the US[19] shows that treatment patterns in patients with mBC have changed following the July 2010 ODAC.

Results indicate that more patients are now offered treatment with combination chemotherapies that are known to carry greater risk for untoward treatment related adverse events, some serious or life threatening. The change in practice pattern raises concerns that the impending FDA action to withdraw the Avastin breast cancer label may be adversely impacting patients' welfare. This concern was noted by Dr. O'Shaughnessy, during the public hearing for Avastin mBC, in response to temporary ODAC member Natalie Campagne-Portis' question on benefit-risk.[20]

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[17] O'Shaugnessy J. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J Clin Oncol 2002, 20(12):2812-2823.

[18] Sparano JA, Vrdoljak E, Rixe O, et al. Randomized Phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2010, 29(20):3256-3263.

[19] Based on a subset of results specific to mBC from a blinded and confidential assessment of oncology treatment practice at clinical sites across the United States, conducted quarterly and compiled (Q2 2010 to Q2 2011) by ZS Associates.

[20] Transcript, July 29, 2011 Public Hearing at 181:14-21.

> *“I think that this [keeping Avastin + paclitaxel available] would be a great benefit to women, particularly those, as I pointed out in my presentation, who have more limited treatment options for their breast cancer, triple negative breast cancer, aggressive, people who need combinations. We would be doing a very great disservice to women to take this [Avastin plus paclitaxel] away from them while this confirmatory trial is being conducted.”*

Genentech, breast cancer experts, the National Comprehensive Cancer Network (NCCN) and the European Medicines Agency (EMA) believe that the results of the E2100 study, supported by the positive treatment effect AVADO and RIBBON1 studies, has demonstrated that Avastin plus paclitaxel provides a meaningful therapeutic benefit to patients over existing treatments for metastatic HER2 negative breast cancer. This is especially true for patients with unfavorable disease characteristics, like aggressive HR+/HER2- or TNBC, who have more limited options and for whom single agent chemotherapy is often deemed insufficient.

Conclusion

While some forms of HER2-negative metastatic breast cancer have a relatively indolent course, many others do not, and require rapid intervention with active regimens. Aggressive HR+/HER2- and TNBC are two such subgroups, affecting a significant proportion of patients with breast cancer who have limited therapeutic options. TNBC is particularly difficult when metastatic, disproportionately affecting younger patients and African Americans, and represents a population for whom no biologically targeted therapies are available. Given that aggressive HR+/HER2- and TNBC patients frequently require immediate symptom relief and/or are at imminent risk of organ failure, Avastin plus paclitaxel represents an important treatment option. The benefit risk analysis for Avastin plus paclitaxel in these types of aggressive breast cancer subgroups can be seen as especially favorable because the medical need for improved efficacy (tumor response, delay in disease progression, one year survival) is great and the risks provide an alternative to overlapping toxicities of chemotherapy drugs given in combination. Taken together, the facts argue for maintaining Avastin plus paclitaxel as an approved therapeutic alternative for aggressive subgroups of HER2-negative metastatic breast cancer based on unmet need and clinical benefit.

APPENDIX D

Discussion Paper: Treatment-Related Mortality in the AVADO and RIBBON1 Studies

August 04, 2011

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

The overall incidence of treatment-related mortality was not different in the AVADO and RIBBON1 studies by treatment arm as was made evident in Genentech's presentation at the June 2011 Hearing. In addition, Genentech presented data demonstrating that the incidence of fatal events with cause of death terms that have been associated with Avastin use was also similar on the chemotherapy + placebo and the chemotherapy + Avastin arms. Genentech included these data in its presentation because CDER, at the July 2010 ODAC, presented fatal events due to these terms, regardless of investigator assignment of causality, exclusively for the Avastin arms and ignoring the chemotherapy-only arms. CDER repeated this focus on individual cases at the withdrawal hearing and suggested that it may continue to focus on these cases in its post-hearing submission.

In order to provide a balanced view of safety from these trials, it is important to acknowledge that *twice* as many patients received Avastin on these studies compared to chemotherapy alone according to the study designs. Therefore, in the evaluation of patient-level narratives, the expectation is that there would be twice as many for Avastin, even if the incidences are the same on the treatment arms.

The tables below further illustrate the balance in incidence of fatal events where the cause of death, as deemed post-hoc and regardless of investigator attribution, was deemed "Avastin-related" according to terms included in the product label. The numbers in the tables reflect CDER's post-hoc attribution of Avastin-related deaths for Avastin-treated patients, presumably based on the clinical study reports, which include individual patient narratives. Genentech applied the same event criteria to all non-MBC deaths in the chemotherapy only arms from the Integrated Safety Summary. The data in the tables indicate that deaths due to these causes occurred on both treatment arms, and their frequency is not greater in the Avastin arms, keeping in mind that twice as many women received Avastin on these studies. Specifically, these rates were: RIBBON1 capecitabine (2.0% chemotherapy v 1.2% Avastin), RIBBON1 taxane (2.9% chemotherapy v 1% Avastin), RIBBON1 anthracycline (1% chemotherapy v 1% Avastin), AVADO (0.9% chemotherapy, 0.8% Avastin).

Information regarding risk factors is also included in the table, acknowledging that attribution of adverse events is always challenging, particularly in the setting of adults with advanced cancer. This point is borne out by the investigator's assessment of whether or not the event was attributed to study drug.

"Avastin-related" terms for causes of death included arterial thromboembolism (ATE), venous thromboembolism (VTE), bleeding, intestinal perforation, wound healing, and cardiac (including cardiopulmonary arrest, cardiogenic shock, cardiac arrest).

"Avastin-Related" Causes of Death in RIBBON1 Capecitabine

Randomization 1:2					
Chemotherapy + Placebo (n=201)			**Chemotherapy + Avastin (n=404)**		
ID#	Cause of Death (As Reported by Investigator)	Relatedness by Investigator	ID#	Cause of Death (As Reported by Investigator)	Relatedness by Investigator
37258	**CEREBRAL ISCHEMIA (ATE)**	NOT	39101	**CARDIOGENIC SHOCK**	NOT
Risk factor: hypertension			*Risk factors: hypertension, diabetes, previous anthracyclines*		
32883	**PULMONARY EMBOLISM (VTE)**	RELATED	48952	**MYOCARDIAL INFARCTION (ATE)**	NOT
Risk factor: cancer			*Risk factorss: hypertension, hyperlipidemia, occurred post-progression in open label phase*		
37701	**HEMOTHORAX (Bleeding)**	NOT	42203	**MYOCARDIAL INFARCTION (ATE)**	NOT
Risk factor: iatrogenic event due to central venous catheter placement			*Risk factors: congestive heart failure, hypertension*		
48458	**PULMONARY EMBOLISM (VTE)**	RELATED	46008	**CARDIO-PULMONARY ARREST**	NOT
Risk factor: cancer			*Risk factors: pacemaker, atrial fibrillation, meds include lidocaine, furosemide, potassium, digoxin, warfarin, previous anthracyclines*		
			40302	**CARDIAC ARREST**	NOT
			Risk factors: diabetes, previous anthracyclines		

"Avastin-Related" Causes of Death in RIBBON1 Anthracycline

Randomization 1:2					
Chemotherapy + Placebo (n=100)			**Chemotherapy + Avastin (n=210)**		
ID#	Cause of Death (As Reported by Investigator)	Relatedness by Investigator	ID#	Cause of Death (As Reported by Investigator)	Relatedness by Investigator
42002	**PULMONARY EMBOLISM (VTE)**	RELATED	45102	**PULMONARY HEMORRHAGE (Bleeding)**	RELATED
Risk factor: hypertension, history of DVT, PE			*Comment: AE occurred after progression and while on 2nd line treatment with capecitabine + Avastin; no details on disease, medications*		
			36355	**PERITONITIS ("Perforation Ilial Ulcer")**	RELATED
Risk			*Comment: AE occurred after progression and while on 2nd line treatment with docetaxel + Avastin; no details on disease, meds or other*		

"Avastin-Related" Causes of Death in RIBBON1 Taxane

Randomization 1:2					
Chemotherapy + Placebo (n=102)			**Chemotherapy + Avastin (n=203)**		
ID#	Cause of Death (As Reported by Investigator)	Relatedness by Investigator	ID#	Cause of Death (As Reported by Investigator)	Relatedness by Investigator
42905	**CARDIO-PULMONARY ARREST**	RELATED	45001	**ABDOMINAL ABSCESS** (wound healing)	RELATED
Risk factors: atrial fibrillation, congestive heart failure, hypertension, meds include digoxin, previous anthracyclines			*Comment: No medical history or concomitant medicines reported*		
48202	**PULMONARY EMBOLISM (VTE)**	RELATED	32806	**GI PERFORATION**	RELATED
Risk factor: cancer			*Comment: malignant ascites, presumed intrabdominal cancer*		
46411	**CARDIO-PULMONARY ARREST**	NOT			
Risk factor: Age 85, hypertension, open-label post progression phase					

"Avastin-Related" Causes of Death in AVADO*

Chemotherapy + Placebo (n=231)			Chemotherapy + Avastin (n=247)		
ID#	Cause of Death (As Reported by Investigator)	Relatedness by Investigator	ID#	Cause of Death (As Reported by Investigator)	Relatedness by Investigator
66340/7953	**SUSPECTED CVA (ATE)**	UNRELATED	92017/7351	**HEMOPTYSIS (Bleeding)**	PROBABLY
Comment: After abnormal CT head scan, investigator discontinued placebo due to "concern for bleeding risk"			*Risk factors: 4.5 cm hilar mass, COPD, prednisolone*		
74985/3014	**PULMONARY EMBOLISM (VTE)**	RELATED	66294/1506	**SUSPECTED GI PERFORATION**	RELATED
Comment: Intestinal metastases by history, hospitalized with abdominal pain, no evidence of GI perforation			*Comment: Pt had active ulcerative colitis prior to and during treatment; developed progressive MBC with abdominal pain, liver metastases, peritoneal cancer;* ***perforation not confirmed***		

* Standard dose Avastin

APPENDIX E

Index of Supporting Documentation Provided in Attachment to Post-Hearing Submission of Genentech, Inc.

Category	Document
References	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.
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	Smith LA, Cornelius VR, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and meta-analysis of randomised controlled trials. BMC Cancer 2010, 10:337.
Other Supportive Material	Andrew Pollack, Medicare Will Pay For Avastin In Treating Breast Cancer, New York Times Prescriptions Blog (June 30, 2011).
	Anna Yukhananov and Alina Selyukh, Medicare Will Keep Covering Roche's Avastin, Reuters, June 30, 2011.
	Avastin Breast Cancer Approval In Spotlight With AVADO. The Pink Sheet DAILY, Wednesday May 11, 2011.

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