

*PROPOSAL TO WITHDRAW APPROVAL FOR THE
BREAST CANCER INDICATION FOR BEVACIZUMAB
(AVASTIN)*

June 29, 2011

*A Matter of Record
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1 PROPOSAL TO WITHDRAW APPROVAL FOR THE 2 BREAST CANCER INDICATION FOR BEVACIZUMAB (AVASTIN) 3 4 5 6 FDA PUBLIC HEARING 7 8 9 WEDNESDAY, JUNE 29, 2011 10 8:00 a.m. to 3:15 p.m. 11 12 13 14 FDA White Oak Campus 15 White Oak Conference Center 16 Building 31, The Great Room 17 Silver Spring, Maryland 18 19 20 21 22	1 Mikkael Sekeres, M.D., M.S. 2 Associate Professor of Medicine Staff 3 Cleveland Clinic Taussig Cancer Institute 4 Department of Hematologic Oncology and 5 Blood Disorders 6 Cleveland, OH 44195 7 8 Wyndham Wilson, M.D., Ph.D. 9 Chief, Lymphoma Therapeutics Section 10 Metabolism Branch 11 Center for Cancer Research 12 National Cancer Institute 13 Rockville, MD 20892 14 15 INDUSTRY REPRESENTATIVE (Non-Voting) 16 Gregory Curt, M.D. 17 U.S. Medical Science Lead, Emerging Products 18 AstraZeneca Oncology 19 Garrett Park, MD 20896 20 21 22
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1 MEETING ROSTER 2 ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting) 3 Frank Balis, M.D. 4 The Louis and Amelia Canuso Family Endowed 5 Chair for Clinical Research in Oncology 6 The Children's Hospital of Philadelphia 7 University of Pennsylvania School of Medicine 8 Philadelphia, PA 19104 9 10 Ralph Freedman, M.D., Ph.D. 11 Clinical Professor 12 Department of Gynecologic Oncology 13 The University of Texas 14 M.D. Anderson Cancer Center 15 Houston, TX 77230 16 17 Brent Logan, Ph.D. 18 Associate Professor of Biostatistics 19 Division of Biostatistics 20 Medical College of Wisconsin 21 Milwaukee, WI 53226 22	1 TEMPORARY VOTING MEMBER 2 Natalie Compagni-Portis, Psy.D. 3 Patient Representative 4 Oakland, CA 94611 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

<p style="text-align: center;">Page 5</p> <p style="text-align: center;">C O N T E N T S</p> <p>1</p> <p>2 AGENDA ITEM PAGE</p> <p>3 Opening Remarks by Presiding Officer</p> <p>4 Karen Midthun, M.D. 6</p> <p>5 Affirmative Presentation by Genentech 6</p> <p>6 Questions by CDER 105</p> <p>7 Questions by Advisory Committee and</p> <p>8 Presiding Officer 144</p> <p>9 Clarifying Questions of Genentech</p> <p>10 Witnesses by Genentech 195</p> <p>11 Advice and Recommendations from</p> <p>12 Advisory Committee Members 204</p> <p>13 Closing Statement by Presiding Officer</p> <p>14 Karen Midthun, M.D. 268</p> <p>15 Adjournment 271</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>	<p style="text-align: right;">Page 7</p> <p>1 begin our presentation, I want to be clear about</p> <p>2 why we requested the hearing.</p> <p>3 We are here today for one purpose, to</p> <p>4 explain why we believe that women with metastatic</p> <p>5 breast cancer are better off if Avastin, in</p> <p>6 combination with paclitaxel, remains an approved</p> <p>7 treatment option. We recognize the complexity of</p> <p>8 this situation and respect that both parties have</p> <p>9 come to divergent conclusions on this important</p> <p>10 issue.</p> <p>11 It's important to highlight that CDER and</p> <p>12 Genentech agree on two fundamental principles:</p> <p>13 First, that the magnitude of improvement in</p> <p>14 progression-free survival observed in E2100</p> <p>15 represents clinical benefit. This reflects CDER's</p> <p>16 progressive thinking that PFS of a certain</p> <p>17 magnitude represents benefit in and of itself.</p> <p>18 CDER's position on PFS will likely result in more</p> <p>19 clinical trials and more timely access of new</p> <p>20 medicines for patients with metastatic breast</p> <p>21 cancer. We are not here to debate that issue.</p> <p>22 We also agree with CDER that the accelerated</p>
<p style="text-align: center;">Page 6</p> <p style="text-align: center;">P R O C E E D I N G S</p> <p>1 (8:00 a.m.)</p> <p>2</p> <p>3 Opening Remarks by Presiding Officer</p> <p>4 DR. MIDTHUN: Good morning and welcome to</p> <p>5 this, the second day of the Avastin hearing. There</p> <p>6 will be a few changes to the schedule today that I</p> <p>7 will note as we proceed throughout the day. But</p> <p>8 now we will proceed to the portion of the hearing</p> <p>9 where Genentech will make its presentation, and</p> <p>10 they have two hours allocated for that. Thank you.</p> <p>11 Affirmative Presentation by Genentech</p> <p>12 DR. BARRON: Good morning. Thank you,</p> <p>13 Dr. Midthun, committee members, FDA representatives</p> <p>14 and guests. My name is Hal Barron. I'm the</p> <p>15 executive vice president of global product</p> <p>16 development and the chief medical officer for</p> <p>17 Genentech Roche. I want to thank Dr. Hamburg for</p> <p>18 granting us this hearing today.</p> <p>19 Yesterday we heard moving testimonies from</p> <p>20 the public as well as comments from CDER on their</p> <p>21 interpretation of the studies evaluating Avastin in</p> <p>22 patients with metastatic breast cancer. As we</p>	<p style="text-align: right;">Page 8</p> <p>1 approval process must be preserved, particularly</p> <p>2 CDER's authority to quickly withdraw products which</p> <p>3 are identified to have new safety concerns or</p> <p>4 products which fail to confirm any benefit in</p> <p>5 subsequent studies, or when sponsors fail to</p> <p>6 conduct the agreed upon confirmatory trials in a</p> <p>7 timely manner.</p> <p>8 However, we disagree on four key points</p> <p>9 which each of our speakers will address in detail</p> <p>10 today. The first point is that Avastin's safety</p> <p>11 profile has been broadly misunderstood based on how</p> <p>12 CDER has presented the data. Avastin has an</p> <p>13 acceptable risk profile for the indication for</p> <p>14 which it is approved.</p> <p>15 Second, E2100 was a well-conducted clinical</p> <p>16 trial with robust results that are clearly</p> <p>17 clinically meaningful.</p> <p>18 Third, the AVADO and RIBBON 1 studies met</p> <p>19 their prespecified primary endpoint with hazard</p> <p>20 ratios less than 0.7, and as such do not invalidate</p> <p>21 the findings of E2100.</p> <p>22 Fourth, the regulations around accelerated</p>

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1 approval anticipated the current situation, a
 2 situation in which a definitive interpretation
 3 cannot be made. In this situation, the regulations
 4 allow for accelerated approval to be maintained
 5 while subsequent studies are conducted to resolve
 6 important issues that remain.

7 The data from E2100 strongly suggests that
 8 patients experience a clinically meaningful benefit
 9 when they receive Avastin in combination with
 10 paclitaxel. Subsequent studies with other
 11 chemotherapeutic agents also demonstrate a benefit
 12 but of a lesser magnitude. One possible
 13 explanation for this observation is that because
 14 paclitaxel and Avastin is a well-tolerated regimen.
 15 Patients can remain on therapy for a longer period
 16 of time and as such experience a more pronounced
 17 treatment effect.

18 This issue needs to be clarified before
 19 concluding Avastin in combination with paclitaxel
 20 is not benefitting women with metastatic breast
 21 cancer. You will hear more about this issue in our
 22 proposed study in the next presentation.

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1 Let's look at each of these four points in
 2 more detail. First, I will focus on safety. In
 3 ODAC presentations and public documents describing
 4 Avastin's effect in patients with metastatic breast
 5 cancer, CDER has repeatedly unfairly characterized
 6 Avastin's safety profile. Misleading comments have
 7 left people with the inaccurate perception that
 8 Avastin is a toxic drug, including an ODAC member
 9 who in 2010 indicated he thought Avastin was
 10 increasing total mortality.

11 Let's look at the data. There are fewer
 12 total deaths and fewer deaths related to metastatic
 13 breast cancer when women were treated with Avastin
 14 in the E2100 study, as you can see here, with the
 15 total mortality difference in absolute terms being
 16 a delta of 3.4 percent. This is true in E2100 as
 17 well in the pooled analysis of all three trials
 18 that include both E2100, the RIBBON 1 and AVADO
 19 studies. As you can see again, there were fewer
 20 total deaths and fewer deaths due to metastatic
 21 breast cancer. Dr. Horning will review this data
 22 in more detail in here presentation to follow.

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1 Second, E2100, as I mentioned, was a well-
 2 conducted clinical trial with robust results that
 3 are clearly clinically meaningful. I'd like to
 4 remind everyone that this study was designed and
 5 implemented by leading breast oncologists in the
 6 United States in collaboration with the National
 7 Cancer Institute, a federally-funded body. The
 8 trial was deemed robust by the New England Journal
 9 of Medicine who published the results, as well as
 10 by most regulatory agencies outside the United
 11 States who based their decision for full approval
 12 based on this study.

13 One of the biggest concerns raised by CDER
 14 related to the potential for bias given the
 15 progression was determined by investigators. To
 16 evaluate this possibility, an independent
 17 radiologic review described as IRF was conducted
 18 with the data shown on this slide.

19 As you can see from the slide, the data from
 20 the IRF and the data from the investigators was
 21 very similar with respect to hazard ratios, you can
 22 see .42 versus .48, with respect to overall

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1 response rates with the delta being 25 versus 28,
 2 as well as the Kaplan-Meier curves, which they look
 3 very similar. Thus based on this data, it is
 4 unlikely that bias represents a significant issue
 5 in interpreting this data.

6 Now let's turn our focus to AVADO and
 7 RIBBON 1. The conversion standard communicated to
 8 Genentech by CDER in February 2008 was that full
 9 approval of Avastin in metastatic breast cancer was
 10 dependent on demonstrating an improvement in PFS
 11 and evidence that survival is not impaired. I've
 12 just reviewed the data demonstrating that fewer
 13 women died when treated with Avastin. The data
 14 shown here demonstrate the PFS was improved in each
 15 of the subsequent studies.

16 You can see examining hazard ratios from
 17 AVADO and RIBBON that a highly statistically
 18 significant and clinically meaningful effect is
 19 present in both studies. This is precisely why we
 20 have concluded that AVADO and RIBBON 1 do not
 21 invalidate the findings in E2100.

22 The conclusion drawn by CDER that the

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1 subsequent studies did not demonstrate meaningful
2 benefit was based on medians. Solely focusing on
3 the median differences is flawed, as they can under
4 or at times overestimate the true treatment effect.
5 In addition, this focus on median differences as
6 the primary method of assessing magnitude of
7 benefit appears to represent a change in CDER's
8 thinking since 2008.

9 Finally, withdrawal is not required under
10 the law. Failure to confirm any benefit in a
11 completed trial may reflect that the drug does not,
12 in fact, offer clinical benefit, and in that
13 scenario, we agree a drug should be withdrawn.
14 This is not the case with Avastin. Benefit was
15 demonstrated in the confirmatory trials but of a
16 lesser magnitude than that what was observed in the
17 original study. And as just noted, the differences
18 in the study design may have reflected unforeseen
19 limitations in the trial design rather than clear
20 evidence of a lack of clinical benefit.

21 In today's presentation, you will hear
22 Genentech's view that the scientific and regulatory

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1 issues at hand call for regulatory flexibility, a
2 middle ground, if you will, of maintaining
3 accelerated approval. I want to emphasize that
4 this path forward is clearly allowed by law and
5 supported by the science. Most importantly, this
6 path forward is in the best interests of patients.
7 It will address a public health need to provide
8 additional treatments for women who are suffering
9 from this incurable disease.

10 We acknowledge the complexity of the
11 decision the Commissioner must make in that the
12 magnitude of benefit is inherently subjective.
13 However, based on all the data generated to date,
14 we believe it is better for women diagnosed with
15 metastatic breast cancer to have the option to
16 receive Avastin in combination with paclitaxel, and
17 many patients, many physicians, the NCCN and EMA
18 agree.

19 Here's the agenda showing our list of
20 speakers who will discuss each of these issues in
21 greater detail. And now I'd like to introduce
22 Dr. Sandra Horning, our global head of clinical

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1 development.

2 DR. HORNING: Good morning. I'm Sandra
3 Horning, global head of clinical development,
4 oncology, hematology at Genentech. I lead the
5 clinical scientists for all oncology products in
6 later stage development.

7 Before coming to Genentech in 2009, I was a
8 practicing oncologist and professor of medicine at
9 Stanford University for more than 25 years. I've
10 also served as a member of the Oncology Drugs
11 Advisory Committee to CDER and as president of the
12 American Society of Clinical Oncology.

13 Let's begin today's discussion in the clinic
14 where an oncologist counsels her patient about the
15 underlying disease, how it is behaving, and what
16 the alternatives for treatment are. The clinical
17 setting we are discussing is HER2-negative
18 metastatic breast cancer, which I will refer to as
19 MBC.

20 In the U.S., about 45,000 people receive the
21 diagnosis of HER2-negative MBC last year. The
22 condition is generally incurable with median

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1 survival times of 18 months to two years. Since
2 1980, a period of 31 years, just two non-hormonal
3 regimens have been approved in the U.S. for the
4 first-line treatment of HER2-negative or HER2
5 unspecified MBC. Gemcitabine plus paclitaxel
6 received full approval in 2004, and Avastin plus
7 paclitaxel was granted accelerated approval in
8 2008.

9 This clinical setting remains an unmet
10 medical need. As you heard in moving testimonials
11 yesterday, women with MBC need more and better
12 treatment options.

13 What are the indications and choices for
14 chemotherapy treatment in MBC? Chemotherapy is the
15 standard of care for patients with hormone receptor
16 negative disease, commonly referred to as triple
17 negative. It's also indicated for the larger group
18 of receptor positive patients for any of the
19 following: for symptomatic or rapidly progressive
20 or visceral disease such as liver or lung or when
21 they become hormonal agent resistant.

22 When it comes to which agents, prior use of

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1 adjuvant chemotherapy by about 60 percent of
2 patients in the U.S. influences treatment choice.
3 Single agents are less toxic and are typically
4 given in sequence as dictated by disease course and
5 tolerability. Chemotherapy combinations are more
6 likely to produce an objective response and disease
7 control so are appropriate for rapidly progressive
8 disease, visceral crisis, or symptom control, but
9 combinations have more overlapping toxicity,
10 particularly low blood counts, and can be difficult
11 to sustain.

12 The key elements of clinical decision-making
13 include the safety profile considered with the data
14 on efficacy. The assessment of clinical benefit
15 risk is always made in context, the context of the
16 clinical setting and the available treatment
17 options. We know that oncologists and individual
18 patients weigh these and other factors differently.
19 In the case of Avastin in MBC, there's scientific
20 debate over the interpretation of the data.

21 While members of ODAC have already expressed
22 their opinion on the issue at the July 2010

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1 meeting, we'd like to engage you today in a
2 discussion of benefit risk in our presentation,
3 expressing Genentech's views on each of these key
4 elements beginning with safety.

5 The data show that Avastin has well-known
6 and acceptable risks for the indication for which
7 it was approved, first-line HER2-negative MBC. Our
8 scientific disagreement with CDER related to
9 Avastin's safety falls into three areas. First,
10 Avastin has been unfairly characterized by CDER as
11 a very toxic drug. The data show that the most
12 common risks are generally manageable, and the
13 Avastin regimen is not more or uniquely toxic
14 compared to other regimens used today for people in
15 this clinical setting.

16 Oncologists are very familiar with Avastin
17 because more than 1 million people have been
18 treated worldwide. This extensive experience
19 extends across five tumor types, including lung,
20 colorectal and breast cancers. There are
21 guidelines for physicians to manage the most common
22 side effects in the package insert. CDER too

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1 agrees that no new signals have been observed in
2 MBC. The difference between CDER and Genentech
3 regarding safety is the interpretation and
4 communication of the data to the ODAC and to the
5 public.

6 Throughout my presentation, I will be
7 referring to the pooled safety analysis involving
8 1,427 MBC patients who received standard dose
9 Avastin. The pooled analysis represents the
10 totality of the safety experience and has been
11 referred to by CDER in their summary argument.

12 The four key points regarding safety are
13 there are fewer deaths on the Avastin-treated arms;
14 there was no difference in treatment-related
15 deaths; the increased select adverse events, AEs
16 greater than grade 3, are predominantly grade 3,
17 and of these the majority are due to manageable
18 hypertension and proteinuria with other select
19 adverse events occurring at low incidence.

20 In particular, there seems to be a
21 misunderstanding regarding deaths in the MBC
22 experience, and this is something I will further

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1 explore with you.

2 The data show that there are fewer total
3 deaths, 52 percent versus 55.8 percent, and fewer
4 MBC deaths, 48.1 versus 51.5 percent, with standard
5 dose Avastin in the pooled safety analysis compared
6 to chemotherapy. And the numbers of non-breast
7 cancer deaths are similar, 3.9 and 4.3 percent.
8 The treatment-related deaths are 1.8 percent in the
9 chemotherapy arm and 1.8 percent in the Avastin
10 plus chemotherapy arms. That is, the incidence of
11 treatment-related deaths are identical in
12 first-line MBC.

13 Now, let's look at the deaths in E2100.
14 Again, there are fewer total deaths on the Avastin
15 arms, and there are fewer MBC deaths on the Avastin
16 arms. The number of non-breast cancer deaths are
17 similar, just as in the larger pooled experience.

18 Treatment-related deaths are not so
19 straightforward in E2100, however. The post hoc
20 assessment of treatment-related deaths that was
21 performed by CDER for the E2100 study, which
22 differed from the study investigators, has caused

<p style="text-align: right;">Page 21</p> <p>1 confusion, and I therefore would like to walk you 2 through the analysis in detail. 3 As we know, attributing deaths to a specific 4 cause is always difficult and subjective, whether 5 by investigator or CDER. However, CDER's 6 assessment was concerning because there were 7 imbalances in the sources of information for the 8 two treatment groups. Per ECOG and NCI standards, 9 only events for the paclitaxel plus Avastin arms 10 were to be entered in NCI AdEERS, the Adverse Event 11 Expedited Reporting System database. That is, 12 events occurring in the paclitaxel-alone arm were 13 not collected because the safety profile of this 14 agent was considered well known. 15 CDER conducted their post hoc assessment by 16 using AdEERS as a source. Their analysis comparing 17 the two treatment arms is based, at least in part, 18 on information collected for just one treatment arm 19 and taking this approach likely introduces bias. 20 And this potential bias becomes apparent when 21 looking at treatment-related deaths across all the 22 studies. Note that for the AVADO and the two</p>	<p style="text-align: right;">Page 23</p> <p>1 percent chance of dying from the complication from 2 their therapy, therapeutic index becomes somewhat 3 different." 4 This interpretation went beyond the ODAC as 5 revealed in this excerpt from the National Cancer 6 Institute bulletin reporting on the July 2010 7 meeting. Speaking of AVADO and RIBBON 1, "In both 8 trials, women in the bevacizumab groups had an 9 increased risk of death. In an analysis of the 10 data prepared by FDA, 0.8 percent of the women in 11 AVADO and 1.2 percent of the women in RIBBON 1 who 12 received bevacizumab died from side effects thought 13 to be related to the drug." 14 Where did this misunderstanding come from? 15 CDER defined a subset of treatment-related deaths 16 as Avastin-related according to specific AE terms 17 which have been associated with Avastin, such as 18 arterial thromboembolism or congestive heart 19 failure. However, and this is a key point, the 20 terms were applied only to the Avastin arms, even 21 though these same adverse events also occurred with 22 chemotherapy alone. In this way, CDER's</p>
<p style="text-align: right;">Page 22</p> <p>1 RIBBON 1 cohorts, the chemotherapy arms had 2 treatment-related deaths on par with the 3 chemotherapy, and yet the analysis for the 4 paclitaxel-alone arm in E2100 stands apart. 5 Nevertheless, we agreed to and have used 6 CDER's E2100 analysis in our product label and in 7 our pooled incidence figures. Despite this, the 8 rates for treatment-related deaths across the MBC 9 experience, 1.8 percent and 1.8 percent, are 10 identical with standard dose Avastin. 11 Now, although these data seem 12 straightforward, CDER's July 2010 ODAC presentation 13 and the subsequent press reports have led to 14 confusion about treatment-related mortality. For 15 example, this is an excerpt from ODAC's discussion, 16 and I quote. "I still do not get a clear picture. 17 Looking at the FDA presentation, there was almost 18 about 1 to 1 and a half percent increase in 19 treatment-related mortality which was maybe related 20 to Avastin with the different chemotherapy arms, 21 whereas in your data, I did not see that. I mean, 22 disease control versus 1 percent or 1 and a half</p>	<p style="text-align: right;">Page 24</p> <p>1 classification of Avastin-related deaths was 2 imbalanced because it was applied to the Avastin 3 arms only. It was not applied to the chemotherapy 4 arms even though deaths occurred due to these AEs 5 such as arterial and venous thromboembolism. 6 Further, CDER emphasized Avastin-related 7 deaths over treatment-related deaths in their 8 communication to ODAC and the public. This 9 characterization led to a misunderstanding that 10 there was a higher treatment-related death rate in 11 the first-line MBC studies. 12 When we look at treatment-related deaths due 13 to these select AEs, we note the familiar Avastin- 14 related death rate of 0.8 to 1.2 percent in the 15 AVADO and RIBBON 1 studies that have been 16 repeatedly highlighted and publicized. However, 17 and please take note, if these same AE terms are 18 applied equally to the chemotherapy arms, a similar 19 incidence of so-called Avastin-related deaths is 20 observed across the AVADO and RIBBON 1 studies. 21 In summary, if you remember one slide about 22 deaths, let it be this one. There were fewer total</p>

<p style="text-align: right;">Page 25</p> <p>1 deaths, fewer MBC deaths, and a similar rate of 2 non-breast cancer deaths in the E2100 study and 3 also in the pooled safety analysis for standard 4 dose Avastin plus chemotherapy. These are the 5 facts regarding deaths in the MBC safety 6 population. 7 We'll now move to adverse events. The 8 tables shows grade 3 to 5 select adverse events, 9 which were collected evenly across all the MBC 10 studies in the pooled analysis of standard dose 11 Avastin. Among the select adverse events, there 12 was a 13.3 percent increase with Avastin plus 13 chemotherapy compared to chemotherapy alone. 14 Hypertension and proteinuria account for much of 15 the increase such that excluding these two more 16 common AEs, when they were the only cause of 17 grade 3 or higher event, results in an overall 18 incidence of 5.6 percent for other AEs. 19 Hypertension and proteinuria, which are 20 related to Avastin's mechanism of action, VEGF 21 inhibition, are well described, and guidelines for 22 monitoring and management are available in the</p>	<p style="text-align: right;">Page 27</p> <p>1 established, and doctors are knowledgeable. 2 Hypertension is a common side effect of 3 Avastin exposure. Monitoring and management are 4 indicated and provided in the package insert. 5 Reversibility is expected, although the subject has 6 been incompletely studied. It has been primarily 7 confirmed by the experience of clinicians. Because 8 the use of Avastin and other VEGF pathway 9 inhibitors is widespread, a National Cancer 10 Institute task force has recently provided 11 management guidelines. 12 The NCI angiogenesis task force published 13 their recommendations in 2010. I'd like to call 14 your attention to three features of this article. 15 First, the authors point out that the goals and 16 approach to blood pressure management in metastatic 17 cancer patients is different compared to a typical 18 hypertensive population due to their reduced life 19 expectancy. Second, hypertension is considered 20 reversible such that discontinuation or dose 21 reduction can be used as a means of control. 22 Third, because blood pressure elevation is a</p>
<p style="text-align: right;">Page 26</p> <p>1 package insert. 2 To refresh your memory, the grading systems 3 for hypertension and proteinuria are described. 4 Note the E2100 study used an older version of 5 toxicity grading such that any treatment for 6 hypertension is considered grade 3, whereas in the 7 other studies, grade 3 was scored for the use of 8 more than one drug. Grade 4 hypertension indicates 9 life-threatening consequences. Grade 3 proteinuria 10 is based on a laboratory measurement of the urine 11 whereas grade 4 proteinuria is a clinical problem 12 known as the nephrotic syndrome. I will speak to 13 each of these adverse events in turn. 14 Hypertension is very common in our society. 15 More than 50 million Americans have hypertension 16 warranting treatment, nearly 1 in 3 over the age of 17 18. Half of our population over age 60 is 18 hypertensive. Two-thirds require more than one 19 drug to manage. That would be similar to the 20 definition of grade 3 used in the AVADO and 21 RIBBON 1 studies as described on the previous 22 slide. Guidelines for treatment are well</p>	<p style="text-align: right;">Page 28</p> <p>1 reversible mechanism-based effect, physicians are 2 advised to anticipate the need to discontinue or 3 reduce anti-hypertensives when treatment ends. 4 What has been the experience with 5 hypertension in MBC? There were no deaths due to 6 hypertension. Grade 4 toxicity was 0.4 percent; 7 that is, five patients in the total experience of 8 1,427. In addition, treatment discontinuation due 9 to hypertension was low at 1.7 percent. 10 Now, let's move to proteinuria. In 11 addition, VEGF leads to changes in the kidney 12 architecture akin to this artistic rendition that 13 result in leakage of the protein albumin in the 14 urine. At the microscopic level, these changes are 15 similar to those seen in the preeclampsia of 16 pregnancy, a VEGF inhibition-related disorder that 17 resolves with delivery of the placenta. 18 In clinical experience, proteinuria 19 typically resolves with Avastin discontinuation, 20 which is in the management guidelines, and 21 proteinuria has not been associated with an 22 increase in creatinine. Preclinical and clinical</p>

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1 evidence indicates that massive proteinuria occurs
2 in people with preexisting kidney disease, such as
3 after nephrectomy where repair and resolution may
4 take longer. These facts strongly suggest that
5 data from renal cell cancer, which is in our
6 product label and has been called out by CDER in
7 the summary argument, may be a special case.
8 In the MBC experience, there were no deaths
9 due to proteinuria in any of the studies. Grade 4
10 toxicity, the clinical nephrotic syndrome, occurred
11 in 0.4 percent or five of the 1,427 patients. The
12 proportion who discontinued treatment due to
13 proteinuria was low at 1.1 percent. We have not
14 observed an association between proteinuria and
15 reduction in glomerular filtration as determined by
16 serum creatinine in any of the MBC studies.
17 Now, next I will present a series of three
18 slides on the time course of proteinuria from the
19 adjuvant colorectal cancer study, CO8, conducted by
20 the NSABP and supported by Genentech. This large
21 2700-patient study provides a prospective
22 evaluation of proteinuria as part of our

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1 postmarketing commitment for Avastin and was
2 highlighted in CDER's summary argument.
3 This slide shows the incidence of
4 proteinuria at any time during the study for
5 chemotherapy or chemotherapy-plus Avastin. The
6 data are displayed by any grade and specific grade.
7 As expected, more proteinuria was seen with
8 Avastin, mainly grade 1, but 2.6 percent had
9 grade 3 or 4 proteinuria. One of the 1,338
10 patients on the Avastin arm had the clinical
11 nephrotic syndrome. We were somewhat surprised by
12 the incidence of grade 1 proteinuria in the
13 chemotherapy arm.
14 I'm now highlighting the 463 control
15 patients and the 728 Avastin patients to discuss
16 the status of their proteinuria at the last study
17 visit on the next slide.
18 The data on this slide illustrate two major
19 findings. First, you see that proteinuria has
20 resolved to grade 1 or zero in more than 96 percent
21 of patients in either treatment arm. Second, you
22 see that grade 2 to 4 proteinuria, which, if not

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1 resolved, could lead to renal impairment in a
2 proportion of patients over a period of years, is
3 very similar in both arms. In sum, 32 of 2700
4 patients in the CO8 trial had grade 2 to 4
5 proteinuria at last study visit, and the actual
6 number of affected patients, 16 and 16, is
7 identical for the chemotherapy and the chemotherapy
8 plus Avastin arms.
9 Just a few weeks ago at the ASCO annual
10 meeting, the CO8 investigators presented their data
11 on the incidence of grade 3 to 4 hypertension and
12 proteinuria between three and nine months after one
13 year of Avastin treatment. These data are from
14 their public presentation. The incidence of
15 hypertension and proteinuria during the study were
16 consistent with the product label.
17 Please note the investigators' report that
18 essentially no differences were observed between
19 the treatment arms for either grade 3 and higher
20 hypertension or proteinuria within 12 months of the
21 completion of Avastin. Together, the large body of
22 evidence from the CO8 trials confirms the

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1 experience of physicians and from several of the
2 patients we heard from yesterday that clinically
3 significant hypertension and proteinuria, VEGF-
4 related side effects of Avastin, are largely
5 reversible upon treatment discontinuation.
6 Returning to MBC, this is a summary of the
7 select adverse events with standard dose Avastin in
8 the pooled analysis. The total is increased from
9 23.1 to 36.4 percent. The 13.3 percent increase is
10 mainly 7.7 percent due to hypertension and
11 proteinuria exclusively. Key to note is that
12 75 percent of the serious AEs are grade 3.
13 Among the 5.6 percent increase due to other
14 causes, the absolute increases for bleeding,
15 congestive heart failure, and arterial
16 thromboembolism range from 1.2 to 1.6 percent. The
17 incidence of other select AEs is less than
18 1 percent in both treatment arms.
19 Yesterday from CDER, we heard an anecdote of
20 fatal GI perforation occurring in the Avastin arm
21 of the AVADO study. Notably, the rate of grade 3
22 to 5 perforation was actually 0.5 percent higher in

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1 the placebo arm of this study. If we look at the
2 pooled analysis, GI perforations occurred in 0.3
3 percent on the chemotherapy arms and 0.5 percent on
4 the chemotherapy plus Avastin arms. The incidence
5 of venous thromboembolism was higher on the
6 chemotherapy arms in the MBC experience.
7 How does this safety profile compare to
8 available treatments for MBC? Multiple serious
9 toxicities are well established for single agent
10 chemotherapies used in first-line MBC. These
11 include kidney, liver, cardiac, respiratory and
12 other toxicities. And when used in combination as
13 for the approved use of gemcitabine plus
14 paclitaxel, there's an increase in adverse events
15 due to both additional and especially overlapping
16 toxicity such as grade 3 and higher increases in
17 neutropenia at 35.4 percent as well as
18 thrombocytopenia, dyspnea, anemia and
19 transaminitis.
20 In summary, Avastin has been shown to have
21 acceptable risks for the indication for which it
22 was approved. There were fewer total deaths on the

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1 Avastin arms and fewer MBC deaths on the Avastin
2 arms. The non-breast cancer deaths and treatment-
3 related deaths are similar. With regard to grade 3
4 and higher AEs, these were primarily grade 3 with
5 7.7 percent increase exclusive to hypertension and
6 proteinuria with reversibility anticipated. A
7 5.6 percent increase in grade 3 or higher other
8 events was seen.
9 Avastin has serious side effects, as
10 described in the product label, but it is not more
11 or uniquely toxic compared to other MBC treatments.
12 Let's turn to efficacy. The next series of
13 slides will establish that Avastin plus paclitaxel
14 is effective in first-line MBC. Importantly, the
15 E2100 study is not invalidated by the results of
16 AVADO and RIBBON 1.
17 We have three areas of scientific
18 disagreement with CDER regarding efficacy. First,
19 we find that E2100 study to be well-conducted with
20 robust results. Second, AVADO and RIBBON 1 are
21 both positive studies. They do not invalidate the
22 E2100 study, and external experts endorse this

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1 position. Third, the chemotherapy partner may
2 contribute to the greater magnitude of effect
3 observed with weekly paclitaxel and Avastin in
4 E2100, and this can be studied in a confirmatory
5 trial.
6 E2100 is a randomized, controlled Phase 3
7 trial that enrolled over 700 patients predominantly
8 from the United States. As such, the study
9 reflects the demographics, comorbidities and
10 standards of practice associated with MBC in this
11 country. E2100 was sponsored by the National
12 Cancer Institute and led by the Eastern Cooperative
13 Oncology Group, one of the largest and most
14 experienced cancer research organizations in the
15 United States. The results of E2100 have been
16 subjected to multiple sensitivity analyses and
17 independent review by CDER.
18 E2100 was one of many cooperative group
19 studies that have met FDA standard for regulatory
20 approval from 1990 to 2008. These studies have
21 influenced the standard of care in multiple tumor
22 types in this country.

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1 Funded by the U.S. government, E2100 has had
2 a global influence. Avastin plus paclitaxel was
3 first approved in Europe in 2007. Currently, this
4 combination is available to women with first-line
5 metastatic breast cancer in 84 countries around the
6 world.
7 Now, let's look at the E2100 study design.
8 As this diagram shows, MBC patients were eligible
9 if they had not received prior treatment with
10 chemotherapy in the metastatic setting. The study
11 was large, 722 patients were randomly assigned to
12 treatment with paclitaxel 90 milligrams per meter
13 squared weekly times three in four-week cycles
14 alone or combined with Avastin at the standard
15 dose. Therapy was continued until disease
16 progression. The primary endpoint was
17 progression-free survival.
18 The E2100 study had 85 percent power to
19 detect a 33 percent increase in PFS from the
20 projected six months to eight months with 685
21 patients and 546 events.
22 Shown here are the primary study results

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1 according to tumor evaluations made by the
 2 independent radiology facility. Approximately half
 3 of the patients had an event progression or death
 4 at the time of the analysis. In the upper right-
 5 hand corner of the plot, you see the hazard ratio
 6 of 0.48 representing a reduction by half in the
 7 risk of disease progression or death. This result
 8 is highly statistically significant. The Kaplan-
 9 Meier curve shows that the median PFS was
 10 11.3 months for the paclitaxel plus Avastin arm and
 11 5.8 months in the paclitaxel arm. Another way to
 12 describe the data is at landmarks. There was a
 13 24.5 percent improvement in PFS at six months and a
 14 20.6 improvement at 12 months.

15 The objective response rate in E2100
 16 effectively doubled with the combination of
 17 paclitaxel and Avastin as reported by investigators
 18 and confirmed by the IRF. In addition, there was a
 19 lower disease progression rate at the first
 20 assessment, a finding that can be important for
 21 patients who need immediate disease control.

22 Overall survival is depicted on this slide.

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1 We see a consistent separation of the curves
 2 favoring Avastin up to 30 months after which they
 3 are overlapping. The hazard ratio for overall
 4 survival is .87, and the median OS was numerically
 5 greater on the Avastin arm, 26.5 versus
 6 24.8 months.

7 Although this study did not demonstrate a
 8 statistically significant improvement in overall
 9 survival, it is incorrect to say that there was no
 10 survival benefit. At one year, there was a
 11 7.4 percent increase in survival, and the
 12 confidence intervals indicate that a modest
 13 improvement is much more likely than no
 14 improvement. At two years, there was a 4.9 percent
 15 increase in survival.

16 For 10,000 women, the survival and PFS data
 17 would translate into 740 more alive and 2,060 more
 18 alive and progression free at one year. The
 19 evidence shown here certainly rules out a detriment
 20 to overall survival and suggests further treatment
 21 benefit beyond the PFS and objective response
 22 improvements.

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1 Now I will transition to a series of slides
 2 that establish that the E2100 results are not
 3 invalidated by AVADO and RIBBON 1.

4 This is an important slide. Prior to the
 5 granting of accelerated approval for Avastin in MBC
 6 in February 2008, Genentech shared the then
 7 confidential top-line AVADO results in a series of
 8 22 slides. One of these is pictured here. At that
 9 time, the PFS results were mature. More than half
 10 had experienced an event. The hazard ratio for the
 11 standard Avastin arm compared to the placebo was
 12 0.64 which was highly statistically significant.

13 Note that the median PFS was 8 months in the
 14 placebo arm versus 8.8 months in the Avastin
 15 standard dose arms. This difference in magnitude
 16 of .8 months clearly did not replicate the
 17 5.5 months in E2100. Nonetheless, CDER granted
 18 accelerated approval for Avastin plus paclitaxel
 19 and accepted AVADO as a confirmatory trial, knowing
 20 that AVADO did not and would not confirm the
 21 magnitude of benefits seen in E2100 if the measure
 22 of magnitude was to be median PFS.

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1 Further, AVADO's PFS and overall response
 2 data were cited in the office director's
 3 accelerated approval memo in February 2008. At
 4 that time, it was noted that the survival data were
 5 immature with fewer than 20 percent of events on
 6 any arm. In addition, in Dr. Pazdur's interview
 7 with the Cancer Letter also in February 2008, AVADO
 8 was described as supporting E2100.

9 These facts led Genentech to understand two
 10 things. First, that CDER considered AVADO to
 11 support the E2100 study based on the magnitude of
 12 the PFS hazard ratio and, two, that the requirement
 13 for confirmation of E2100 would be a demonstrated
 14 improvement in progression-free survival without a
 15 detriment in overall survival.

16 If Genentech had known that the requirement
 17 for conversion was 5.5 months median PFS, we would
 18 have designed a confirmatory trial with paclitaxel
 19 plus Avastin in 2008 because both CDER and
 20 Genentech knew that the results with docetaxel plus
 21 Avastin in AVADO had not replicated the magnitude
 22 of median PFS seen in E2100.

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1 Reviewing the same data as CDER, the
2 European Commission came to the opposite
3 conclusion. They retained approval for Avastin
4 plus paclitaxel in February 2011. This ruling
5 followed the advice of the Committee for Medicine
6 Products for Human Use, CHMP, which made these
7 statements in December 2010. "The available data
8 have convincingly shown bevacizumab to prolong
9 progression-free survival of breast cancer patients
10 without a negative effect on the overall survival."
11 And, "The benefits of Avastin with paclitaxel
12 outweigh its risks, and the combination remains a
13 valuable treatment option."
14 The CHMP did not consider the AVADO and
15 RIBBON 1 studies to invalidate E2100. Rather, they
16 stated, "Avastin has been convincingly shown to
17 prolong PFS without a negative effect on OS, and
18 the new study data support this conclusion."
19 Another influential scientific body
20 determined that the E2100 results were not
21 invalidated by AVADO and RIBBON 1. The National
22 Comprehensive Cancer Network, NCCN, unanimously

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1 affirmed Avastin plus paclitaxel for first-line MBC
2 in October 2010. As can be seen on the list on the
3 right, NCCN represents the nation's top cancer
4 centers for treatment and research. The NCCN
5 guidelines, which are highly influential in the
6 practice of oncology, are updated by an evidence-
7 based process that involves explicit review of
8 scientific evidence by expert physicians.
9 The NCCN breast cancer panel members
10 specialize in breast cancer. They have their
11 primary, if not exclusive, practice in breast
12 cancer, and they are active breast cancer
13 researchers and educators. Twenty-seven panel
14 members participated in the Version 2.2011
15 recommendation.
16 The NCCN panel reviewed the same studies as
17 CDER, meeting in person or by phone on three
18 occasions to discuss Avastin plus paclitaxel in MBC
19 in the five months leading to FDA's withdrawal
20 proposal. This resulted in a unanimous decision to
21 affirm a recommendation for Avastin with paclitaxel
22 as a preferred partner.

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1 Now let's turn to the data across the first
2 line MBC studies. Here are the forest plots for
3 the E2100 AVADO and RIBBON 1 studies, showing a
4 consistent PFS improvement with Avastin. Each was
5 a positive study that exceeded its primary PFS
6 endpoint with target hazard ratios of .7 to .75 in
7 favor of Avastin and had been agreed upon as
8 supplemental biologic license applications to
9 support conversion. If you look at the hazard
10 ratios for AVADO and RIBBON 1, you note that they
11 bracket the .65 hazard ratio for gemcitabine plus
12 paclitaxel, which is fully approved in first line
13 MBC.
14 As we stated in July 2010, the hazard ratios
15 in these studies are not statistically different.
16 The medians, which may not reliably reflect
17 treatment effect, look far more different from one
18 another. The hazard ratios in these studies ranged
19 from 0.48 to 0.69. This could be due to chance or
20 could reflect a difference in chemotherapy partner
21 or exposure in combination with Avastin.
22 If we now understand that the measure of

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1 magnitude is median PFS and that the E2100 result
2 must be replicated, then it is important to
3 maintain the treatment conditions exactly as
4 feasible and incorporate paclitaxel as the
5 chemotherapy partner.
6 The next series of slides relates to
7 statements and actions related to chemotherapy
8 partner for Avastin and the available scientific
9 data on the subject. Both the European and NCCN
10 decisions indicate that chemotherapy matters, as
11 illustrated in this table. The importance of
12 chemotherapy partner is highlighted by the
13 different actions taken in Europe with regard to
14 the taxanes, reaffirming paclitaxel but choosing to
15 withdraw docetaxel upon further review based on
16 clinical study data. The EMA also issued a
17 positive opinion for full approval for capecitabine
18 with its hazard ratio of 0.69 and median PFS of 2.9
19 months based on the RIBBON 1 data.
20 CDER has previously expressed the view that
21 treatment results may vary by chemotherapy in
22 several communications to Genentech. At the 2006

<p style="text-align: right;">Page 45</p> <p>1 Type B meeting, FDA recommended that Genentech 2 consider separate studies with the individual 3 chemotherapy agents in the Avastin MBC study 4 because their treatment affect will vary according 5 to the chemotherapy regimen used. Of course, the 6 Avastin indication for MBC was limited to 7 paclitaxel as the sole chemotherapy partner. 8 In the laboratory, multiple models show an 9 enhanced anti-tumor effect with Avastin combined 10 with chemotherapy. In these models, the taxanes 11 have equal or greater efficacy than other 12 chemotherapy agents. A consistent finding has been 13 that longer exposure of Avastin plus chemotherapy 14 increases efficacy. In the clinic, many 15 practitioners favor weekly paclitaxel because it is 16 well tolerated. In addition, greater efficacy has 17 been seen in some Phase 3 studies comparing weekly 18 to intermittent schedules of paclitaxel in early 19 and metastatic breast cancer. In contrast, 20 docetaxel duration is limited by toxicity. 21 In a recent meta-analysis, longer duration 22 of chemotherapy led to greater efficacy. Most</p>	<p style="text-align: right;">Page 47</p> <p>1 greater dose intensity prior to disease progression 2 compared to docetaxel in the two studies. 3 Weekly paclitaxel provides more frequent 4 exposure, and this has been linked to greater 5 antiangiogenic activity in the preclinical setting. 6 Together, these data are consistent with less 7 overlapping toxicity and greater tolerability of 8 paclitaxel in the clinic. The clinical data 9 suggest that weekly paclitaxel plus Avastin is more 10 effective because combined exposure is greater, and 11 this can be confirmed with an additional study. 12 Placing the efficacy data together, we find 13 that E2100 is a well-conducted trial with robust 14 results that are not invalidated by AVADO and 15 RIBBON 1. Accelerated approval was granted with 16 the definitive AVADO PFS data. Europe and NCCN 17 reaffirmed the paclitaxel results, and AVADO and 18 RIBBON 1 are positive studies. Multiple lines of 19 evidence indicate that chemotherapy exposure 20 partner may matter. 21 Now let's go back to the clinic. For the 22 assessment of benefit risk in this indication, I</p>
<p style="text-align: right;">Page 46</p> <p>1 pertinent to today's discussion, in the Avastin MBC 2 trials, greater efficacy was observed with 3 paclitaxel in the E2100 study. 4 Is it biologically plausible that paclitaxel 5 is a preferred partner for Avastin? Let me go 6 through some of the data from our MBC trials 7 demonstrating greater exposure for paclitaxel 8 compared with docetaxel. 9 We observed a longer treatment duration with 10 paclitaxel, the white dotted line, compared to 11 docetaxel in the AVADO, golden line, and RIBBON 1, 12 blue dotted line, studies, 8.4 versus 5.5 and 4.7 13 months. The proportion of patients on treatment at 14 12 months was 30 percent for paclitaxel versus 15 zero percent and 8.5 percent. These observations 16 are admittedly difficult to separate from treatment 17 effect. 18 However, we also find that there was less 19 discontinuation due to toxicity prior to disease 20 progression with paclitaxel compared to docetaxel 21 in RIBBON 1 at 27 weeks or longer, 27 percent 22 versus 59 percent. Paclitaxel was associated with</p>	<p style="text-align: right;">Page 48</p> <p>1 present the pooled safety, representing the 2 totality of the MBC experience and the E2100 3 efficacy data in a way that would allow physicians, 4 patients, and health authorities to assess and 5 contrast each element in clinical decision-making. 6 With regard to deaths, there were fewer 7 overall MBC deaths with Avastin, and treatment- 8 related mortality is equal in the pooled analysis. 9 There's a 13.3 percent increase in select grade 3 10 or higher AEs, 7.7 percent exclusively due to 11 hypertension and proteinuria, and 5.6 percent due 12 to other causes in the pooled safety analysis. 13 The efficacy data for E2100 are listed on 14 the right. For survival, there's a 7.4 percent 15 increase at one year and 4.9 percent increase at 16 two years. For PFS, there's a 24.5 percent 17 increase at six months and a 20.6 percent increase 18 at 12 months. A 28 percent increase, more than a 19 doubling, was observed in response rate. 20 These data demonstrate a favorable benefit 21 risk for paclitaxel plus Avastin. But we also seek 22 to do better by defining a biomarker for patients</p>

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1 who may achieve greater benefit. Dr. Reimann will
2 discuss this further in his talk, but I will
3 introduce the subject.
4 Angiogenesis in tumors involves a complex
5 interaction between tumor, stroma, and many pro and
6 antiangiogenic factors as captured by this figure.
7 This complexity creates considerable challenges for
8 biomarker discovery.
9 Since 2002, Genentech and Roche evaluated
10 more than 100 potential markers in clinical
11 specimens of plasma, tumor, and host DNA across
12 seven tumor types. Data from more than 10 phase 3
13 trials with adequate sample collections began to
14 read out in 2010 and will continue through 2012.
15 Naturally, VEGF pathway markers have been a major
16 focus in this work based on the mechanism of action
17 of Avastin.
18 This slide summarizes the current status of
19 our biomarker research, focused on predicting which
20 patients will benefit from Avastin and which
21 patients may be at greater risk for adverse events.
22 Our narrowed candidate list is displayed according

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1 to the type of tissue assayed. Based upon
2 extensive work to date, the key candidates are
3 highlighted in yellow.
4 For breast cancer, based on data from the
5 AVADO trial and other tumor types, the leading
6 predictive biomarker candidate is VEGF-A, the
7 target of Avastin, and Dr. Reimann will detail the
8 methods and analyses leading to this selection.
9 In closing, based upon acceptable safety
10 risks and demonstrated efficacy, we interpret the
11 benefit risk for Avastin plus paclitaxel in MBC to
12 be favorable, and expert scientific bodies agree
13 with this interpretation. In the context of an
14 incurable disease and the available treatments,
15 which we believe constitute an unmet need, and
16 certainly this is what we heard from the
17 testimonies yesterday, it is best for patients to
18 continue to have this treatment option.
19 This is the argument for maintaining
20 accelerated approval while a new confirmatory
21 trial, one that replicates E2100 with the
22 paclitaxel partner and includes a biomarker

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1 hypothesis to better define clinical benefit, is
2 conducted.
3 I thank you for your attention and invite
4 Dr. Reimann to the podium.
5 DR. REIMANN: Good morning. I'm James
6 Reimann, global head of oncology biostatistics at
7 Genentech Roche. Today I'll be addressing two
8 topics, the robustness of the E2100 PFS results and
9 the design of the proposed confirmatory study of
10 Avastin combined with paclitaxel.
11 We start with robustness of E2100 PFS
12 results by which I mean that the E2100 results were
13 not unduly affected by designs -- concerns about
14 study conduct or analysis methods. At the ODAC in
15 2007 and again more recently, CDER has raised
16 several concerns about E2100 related to the open
17 label design, missing data, variability in tumor
18 assessment, and a more recent question about
19 whether the E2100 data could represent a random
20 high.
21 I will walk you through our careful
22 assessment of these concerns which show that they

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1 are not unusual in breast cancer studies and that
2 there was no evidence of bias.
3 Second, I will review the design and
4 timelines of the proposed confirmatory study of
5 Avastin in combination with paclitaxel.
6 First, robustness. We have carefully
7 assessed the E2100 PFS data with regard to the four
8 concerns shown on the left. I'll address each of
9 these concerns with two critical questions in mind.
10 The first question is whether the concern is out of
11 line with well-accepted breast cancer studies. I
12 will do this by considering the phase 3 studies of
13 various medicines for breast cancer. The second
14 question, at the right, is whether this concern led
15 to any evidence of bias.
16 To start with point 1, let's look at the
17 open label nature of E2100. In contrast to many
18 other disease areas, open label studies are common
19 in oncology. In fact, 78 percent of ongoing
20 phase 3 studies in metastatic breast cancer found
21 on clinicaltrials.gov are open label. As a result,
22 open label studies have commonly served as the

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1 basis of approval for medicines treating metastatic
2 breast cancer, including Herceptin, Gemzar, Tykerb
3 and Ixempra, among others. I will be using these
4 medicines as examples in my presentation to help
5 assess the E2100 data and to place the issues that
6 CDER has raised in the context of breast cancer
7 experience.

8 We performed multiple sensitivity analyses
9 to assess whether there was any evidence of bias in
10 the tumor assessments in E2100. We saw balance in
11 timing of scans with actual scan times matching
12 closely with planned scan times. We saw balance in
13 the percent completeness of scans. Finally, we saw
14 balance in the proportion of patients who
15 discontinued the study without disease progression
16 whether due to toxicity or other reasons. But the
17 most definitive assessment of whether there could
18 have been bias in the tumor assessment was by
19 comparing the PFS results from the investigators
20 and the independent assessment.

21 Shown here are the PFS results as assessed
22 by ECOG investigators. As requested by CDER, we

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1 performed a fully independent review of tumor
2 assessments with the results added here. The two
3 PFS curves for the Avastin arm are identical. The
4 control arm curves are also identical up to eight
5 months.

6 No matter how we look at these data, whether
7 it's differences in medians, hazard ratios or
8 increase in objective response rate, the magnitude
9 of benefit here was substantial and virtually
10 identical between the ECOG investigators and the
11 independent review. So we can say confidently that
12 we found no systematic bias in the E2100 PFS
13 results. This result was, in fact, expected.

14 In late 2009, the FDA hosted a workshop on
15 the topic of PFS in oncology studies in partnership
16 with the DIA, PhRMA, other regulatory authorities,
17 and academic researchers. One outcome of this
18 workshop was the largest ever meta-analysis of
19 investigative versus independent PFS results in 27
20 studies in solid tumor indications. This analysis
21 compared the PFS hazard ratios by investigator and
22 independent review and found no systematic

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1 difference. We see tight agreement in the scatter
2 part shown at right in which E2100 is indicated as
3 the gold circle. Importantly, they also found no
4 difference in the results between blinded studies
5 and open label studies. So the similarity of
6 investigator and independent results for E2100 was
7 completely expected.

8 We have seen that the open label design of
9 E2100 is typical for studies in breast cancer and
10 found no evidence of bias due to this aspect of the
11 design.

12 Now we turn to point 2, missing data. CDER
13 has expressed concern that 10 percent of patients
14 did not have scans for independent review, and
15 34 percent of patients were censored in the PFS
16 endpoint. Given that the independent review in
17 E2100 was retrospectively performed, we were very
18 pleased that 90 percent of the scans were available
19 for independent review. The rate of missing scans
20 in the pivotal study of Tykerb was also 10 percent,
21 and thus the experience with E2100 is not unusual.

22 Importantly, the rate of missing data in

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1 E2100 was identical between the two study arms,
2 90 percent versus 90 percent, and the baseline
3 characteristics of patients with and without scans
4 were similar. Thus, this amount of missing data is
5 both expected and not anticipated to cause bias.

6 The second issue raised by CDER is censoring
7 of the PFS endpoint by which I mean that 34 percent
8 of patients were censored more than 90 days before
9 database cutoff. Although CDER raises as a
10 specific concern for E2100, this amount of
11 censoring has been seen for another breast cancer
12 medicine.

13 In the Phase 3 study of Tykerb, 31 percent
14 of patients were censored more than 100 days before
15 the database cutoff. If the same 90-day cutoff had
16 been used as in E2100, the percentage would have
17 been higher. But most importantly, both the
18 frequency and reason for censoring were balanced
19 between study arms, as shown here. Note also in
20 the first line of the table that one of the most
21 frequent reasons for censoring was use of
22 non-protocol cancer treatment, which was balanced

<p style="text-align: right;">Page 57</p> <p>1 by treatment arm. This was included in the 2 progression-free survival definition in the study 3 analysis plan that was reviewed and agreed to CDER 4 prior to the primary study analysis. 5 We saw that the amount of missing data in 6 the independent review in E2100 was comparable to 7 an approved breast cancer medication and balanced 8 by study arm. 9 Point 3, variability in scan interpretation. 10 First, let me explain how independent review was 11 performed in E2100 using what is called a two- 12 reader format. Six hundred and forty-nine patients 13 had scans for independent review, and two 14 radiologists, which I'll call Reader 1 and 15 Reader 2, assessed these scans in accordance with 16 the RECIST criteria and came up with their 17 conclusions. The IRF checked whether these two 18 readers agreed on progression status and date and 19 objective response status and date. In the event 20 of agreement, those results were used for analysis, 21 which occurred in 55 percent of cases. For those 22 not agreed on, a third radiologist reviewed the</p>	<p style="text-align: right;">Page 59</p> <p>1 "CDER continues to gain experience regarding the 2 reliability of radiographically-determined disease 3 progression, and at this time does not have 4 sufficient experience to say whether the 34 percent 5 rate of discordance between two radiologists is 6 unusual." 7 Given the lack of available data, a group of 8 prominent statistical researchers at NIH looked 9 into this further and published their findings in 10 2010. They assessed possible bias and variability 11 in the hazard ratio by performing a simulation 12 study. What they found was that the amount of bias 13 is extremely small, and, importantly and 14 unexpectedly, this bias favors the control arm, not 15 the experimental arm. They also used the data from 16 E2100 IRF publication in JCO as an example, and 17 they found with the amount of differing assessment 18 in E2100, they would have expected a bias of 19 between .01 and .02 in the estimated hazard ratio 20 in favor of the control arm. 21 So, in summary, although inter-reader 22 differences at the IRF do have some variability,</p>
<p style="text-align: right;">Page 58</p> <p>1 data. 2 I will focus on the cases where there was 3 disagreement in progression status and progression 4 date, which was observed in 34 percent of patients 5 and features in CDER's ODAC briefing books and 6 presentations. 7 Now, it is difficult to assess whether this 8 amount of disagreement, 34 percent, is expected 9 because this level of detail is not normally 10 disclosed in study manuscripts and has not been 11 publicly disclosed for other breast cancer 12 medications. But one way that we can assess it is 13 by looking at the opinion of the adjudicator. 14 The third radiologist assessed the reads by 15 the two primary radiologists, and in 98 percent of 16 cases, agreed with one of the primary readers. 17 This means in 98 percent of cases, they decided 18 that both the choice of lesions and the assessments 19 from one of the primary readers were appropriate 20 and should stand as the final read. 21 CDER was aware back in 2007 that there was 22 not great experience on this issue, as quoted here.</p>	<p style="text-align: right;">Page 60</p> <p>1 this would tend to bias against the novel medicine. 2 A second issue raised by CDER was 3 differences between the investigator and 4 independent reviews in E2100. Now, these 5 differences are expected because of different 6 choices in lesions and images, use of 7 nonradiographic data, and perceptions about new 8 lesions, which can be small. We now have published 9 examples of expected discrepancy rates in many 10 studies with the results from a number of breast 11 cancer studies shown at the right. 12 The agreement rates on progression status 13 and date for E2100 were virtually identical to that 14 observed for the pivotal studies of Tykerb and 15 Ixempra. And these pivotal studies used a 16 two-reader independent review very similar to that 17 used in E2100. And both of these studies received 18 full approval based on their progression-free 19 survival results. 20 In addition, the discrepancy rates in E2100 21 were identical by study arm. The agreement rates 22 were 76 versus 76 percent and 49 versus 49 percent.</p>

<p style="text-align: right;">Page 61</p> <p>1 So again we find these differences are expected, 2 and there is no evidence of bias. 3 Last, we address an issue that CDER raised 4 just last December, that the E2100 results could 5 represent a random high. Reading from CDER's 6 December decision memo, "It is possible that the 7 magnitude of effect observed in E2100, based on the 8 interim analysis, represents a random high and that 9 the true effect is more consistent with a smaller 10 effect seen in the other trials." We examined this 11 issue carefully, and we found no evidence of bias. 12 There is an extensive literature about bias 13 in estimates arising from interim analyses dating 14 back to early work by Scott Emerson and Tom Fleming 15 in the early '90s. As shown by the following 16 quotes, the impact for a well-designed study that 17 reports results with more than 50 percent of events 18 is very small. "Estimates from a trial stopped 19 early for efficacy have negligible bias. Such 20 estimates on average are therefore correct. For 21 trials with a well-designed interim monitoring 22 plan, stopping at 50 percent or greater information</p>	<p style="text-align: right;">Page 63</p> <p>1 free survival results. More importantly, we found 2 no evidence of bias arising from any of these 3 points. 4 The concerns raised by CDER were addressed 5 by Genentech in a detailed submission in 6 December 2007, two months before the issuing of the 7 accelerated approval decision. Quotes from CDER in 8 Dr. Pazdur's office director's memo that 9 accompanied this approval are here. "The current 10 application demonstrates a robust effect on PFS and 11 response rate. Prespecified sensitivity analyses 12 corroborate the maintenance of a treatment effect 13 in handling missing data. Recent applications have 14 had missing data similar to that observed in the 15 current Avastin application, and because of the 16 close agreement between the two assessments, 17 investigator, and IRF, systemic bias seems 18 unlikely." 19 Based on the findings that I've shown you 20 today, we agree with their assessment and stand 21 behind the robustness in substantial magnitude of 22 the E2100 PFS results.</p>
<p style="text-align: right;">Page 62</p> <p>1 has a negligible impact on estimation." 2 We confirmed this in E2100 by calculating 3 adjusted estimates of the hazard ratio using 4 commonly used adjustment methods. We found 5 negligible bias in E2100 in the hazard ratio in the 6 third or fourth decimal place, which would not 7 change any results you see in these slides. 8 In addition, the estimated PFS hazard ratio 9 in E2100 was very precise because this study had 10 the narrowest confidence interval around the hazard 11 ratio estimate of all of the studies of Avastin and 12 first-line metastatic breast cancer. So it is 13 incorrect to assert that E2100 and the results may 14 have been less accurate due to interim data. 15 So in summary, we have carefully assessed 16 each of the points raised by CDER during the 2007 17 ODAC and again more recently. In each case, we 18 find that these points are present in the pivotal 19 studies of breast cancer medications. In fact, all 20 four of these issues were present to a similar 21 degree in the pivotal study of Tykerb, which 22 received full approval based on its progression-</p>	<p style="text-align: right;">Page 64</p> <p>1 Now we change gears. Given Issue 3 before 2 this hearing, the question remains what a study to 3 confirm the magnitude of benefit of Avastin in 4 combination with paclitaxel would look like. I 5 will review the confirmatory study design and 6 timeline, feedback received from CDER in February 7 of this year, and the data supporting the biomarker 8 component of the study. The study schema is shown 9 here. 10 This study is intended to confirm the 11 magnitude of benefit in E2100 and closely matches 12 the design of E2100. The study population is 480 13 patients with HER2-negative metastatic breast 14 cancer who have not received prior chemotherapy. 15 Randomization will be stratified by plasma VEGF-A 16 level, prior adjuvant therapy use, and hormonal 17 receptor status. 18 The treatment regimens are identical to 19 E2100 with standard weekly paclitaxel and Avastin 20 or placebo continued until progression and with no 21 crossover. The study has two primary endpoints, 22 progression-free survival in all patients and</p>

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1 progression-free survival in patients with high
2 plasma VEGF-A, which I will elaborate further.
3 The first and most important objective,
4 shown on the left, is to confirm the magnitude of
5 effect seen in E2100 in the overall study
6 population which could lead to full approval in the
7 overall population. The second objective, on the
8 right, is to validate a method of selecting
9 patients with greater clinical benefit on Avastin
10 using plasma VEGF-A. I will first focus on the
11 overall population objective.
12 For the primary analysis of PFS in all
13 patients, we are targeting 326 PFS events which
14 gives 85 percent and 99 percent power to detect a
15 hazard ratio of .67 or .5. This study will have a
16 smaller number of patients and a smaller number of
17 events than E2100 because we are targeting a
18 greater treatment effect.
19 We expect that this study will predominantly
20 be enrolled outside the United States. The
21 preliminary feasibility assessment is based on
22 prior studies of Avastin in first-line metastatic

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1 breast cancer, the experience of our global CRO,
2 and a country-specific survey of interest in this
3 study. We intend to start this study as soon as
4 possible and to provide results to FDA as soon as
5 possible.
6 We believe that this can best be done
7 through an interim analysis of PFS for the purpose
8 of regulatory futility. By regulatory futility, I
9 mean an early analysis of the data to see whether
10 the benefit seen in E2100 is likely to be
11 confirmed. If the futility boundary is crossed,
12 this analysis could trigger an early voluntary
13 withdrawal of the accelerated approval by
14 Genentech.
15 We propose that this analysis be conducted
16 at 220 PFS events, three and a half years after the
17 start of the study with a final PFS analysis
18 following one year later. A more detailed
19 feasibility assessment is ongoing, and we'll give
20 results very shortly, to determine the best
21 locations for the study and to further refine the
22 enrollment rates and the timeline.

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1 Let me tell you a bit about the regulatory
2 history of the study to better understand the
3 timeline and the FDA feedback we received. So
4 going from left to right, in July 2010, ODAC voted
5 that AVADO and RIBBON 1 were not considered to have
6 confirmed E2100. One month later, Genentech
7 submitted a proposal to CDER for a new confirmatory
8 study of Avastin combined with paclitaxel. CDER
9 granted a Type B meeting to discuss the high level
10 Phase 3 design, which was held in February of this
11 year and to which I will return in a moment.
12 Coming up, CDER has asked us to meet with
13 CDRH, the Center for Devices and Radiologic Health,
14 to discuss the VEGF-A test prior to starting a
15 special protocol assessment with CDER, abbreviated
16 here at SPA, in the fall. We are planning for the
17 first patient to be enrolled in Q1 next year.
18 A central question at the Type B meeting was
19 whether the new study would support full approval
20 of Avastin in combination with paclitaxel. The key
21 quotes from the meeting are shown here.
22 CDER clearly states that repeating the

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1 magnitude of PFS benefit from E2100 combined with
2 no detriment to overall survival would support full
3 approval of Avastin in this setting. So we now
4 have clarity from CDER on a path to full approval.
5 Nevertheless, we have heard from some members of
6 ODAC and some members of the wider oncology
7 community, including yesterday, that new breast
8 cancer medicines need to prolong overall survival.
9 To respond to your perspective, let's review
10 what overall survival data as seen with available
11 medicines in first-line metastatic breast cancer
12 and what it takes to optimally power studies to
13 detect an overall survival benefit in this setting.
14 There are only two non-hormonal medicines
15 approved by FDA since 1980 for the first line
16 treatment of HER2-negative or HER2 unspecified
17 metastatic breast cancer, Avastin in 2008
18 accelerated approval and Gemzar full approval,
19 2004. Neither of these medicines have demonstrated
20 a statistically significantly improved overall
21 survival.
22 What about Gemzar, which was cited by CDER

<p style="text-align: right;">Page 69</p> <p>1 in the 2007 and 2010 ODACs and in their December 2 memos? So let's look at the data. 3 The pivotal study of Gemzar included 529 4 patients who received either paclitaxel alone or in 5 combination with Gemzar. This open label study had 6 co-primary endpoints of overall survival and time 7 to progression, with overall survival tested at the 8 .03 level, which means you need to see a p value 9 smaller than .03 to be statistically significant. 10 This study showed significantly improved 11 time to progression, shown here, and the company 12 approached CDER about a possible submission. CDER 13 allowed the company to perform two unplanned 14 interim survival analyses to support a possible 15 submission. The results of the second interim 16 analyses of survival are shown here. 17 The p value of .049 did not meet the cutoff 18 of .03 specified in the protocol. And, in fact, 19 CDER found p values of greater than .05 in multiple 20 sensitivity analyses. The conclusion of the CDER 21 reviewers was that this data did not show a 22 significant survival benefit but rather represented</p>	<p style="text-align: right;">Page 71</p> <p>1 similar to the interim overall survival results for 2 Gemzar. And the final overall survival results 3 prespecified in each study protocol were very 4 similar with regard to hazard ratio and degree of 5 statistical confidence. 6 So after benchmarking the E2100 results 7 against the gemcitabine, we are confident that a 8 clinically meaningful benefit will be demonstrated 9 in a confirmatory study. 10 So talking about overall survival benefits, 11 everybody here, FDA, ODAC, Genentech, patients, we 12 are all working to prolong survival in patients 13 with metastatic breast cancer. Now, this may come 14 from a large and profound effect in a single study 15 with a single agent, or this may come from a 16 combined PFS effect across multiple agents in 17 first-, second- and third-line setting. But it 18 will not come if we do not do the studies, and the 19 studies are too large and too unfeasible. And it 20 is our position that a strict requirement for new 21 medicines to demonstrate significantly improved 22 overall survival would greatly impact feasibility</p>
<p style="text-align: right;">Page 70</p> <p>1 a strong trend. Gemzar did receive full approval 2 based on these data, but CDER did not allow the 3 survival data, the survival numbers, to be included 4 in product labeling. 5 When the protocol-specified final analysis 6 was performed, as shown here, it was again not 7 significant with a p value of .12, and these 8 results are today included in the product label. 9 This study demonstrates that a 2.3-month 10 improvement in median survival accompanied by a 11 trend in overall survival was considered clinical 12 benefit in this setting. 13 Put side by side, we see that the E2100 data 14 compare favorably to Gemzar, helping us to 15 understand that the E2100 data also demonstrates a 16 meaningful clinical effect. In the larger E2100 17 study shown at the right, the magnitude of PFS 18 improvement is greater, both as a hazard ratio and 19 as a difference in medians. 20 The interim overall survival results that 21 were provided in the initial sBLA of Avastin in 22 breast cancer, shown in the middle row, were very</p>	<p style="text-align: right;">Page 72</p> <p>1 of studies in this setting. This is because in the 2 first-line setting, it is very difficult to 3 optimally power studies to see overall survival 4 benefit. 5 Why is this? The key reason is because 6 survival after first line progression is especially 7 long in breast cancer. We know from multiple long- 8 term studies that overall survival has been getting 9 longer in metastatic breast cancer. This is likely 10 due to the combined effects of better diagnosis, 11 new medicines such as the taxanes, and better 12 supportive care. 13 Importantly, two-thirds or more of a 14 patient's survival time is after their progression 15 on first-line treatment. During this time, 16 patients typically receive multiple subsequent 17 therapies which are not controlled by study 18 protocols and can differ between treatment arms. 19 These therapies add variability, certainly, but 20 also possible bias. 21 Because of this long survival, a similar 22 absolute benefit in PFS and overall survival</p>

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1 measured in months translates into a much smaller
2 relative benefit in overall survival measured by
3 the hazard ratio. For example, a four-month
4 improvement in median PFS from 6 to 10 months is a
5 67 percent improvement, while a four-month
6 improvement in median overall survival from 24 to
7 28 months is a 17 percent improvement.
8 This dilution of the overall survival hazard
9 ratio compared to the PFS hazard ratio has been
10 noted in several publications; and because studies
11 are powered based on hazard ratios, not based on
12 medians, it means we need much larger clinical
13 studies to optimally power for overall survival
14 benefits in first-line metastatic breast cancer.
15 This means that typical studies in the front-line
16 setting, which are enrolling about 500 to 800
17 patients, are not optimally powered for overall
18 survival.
19 This is an important point. Although they
20 may be fully powered for a large overall survival
21 benefit such as eight months, they are underpowered
22 to observe benefits on the order of three to four

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1 months, which may still be clinically meaningful
2 and clinically interesting.
3 In summary, a strict requirement to
4 demonstrate statistically significant overall
5 survival in first-line metastatic breast cancer
6 would greatly impact feasibility of studies. And
7 CDER has exercised regulatory flexibility on this
8 issue in the past, approving agents in the
9 refractory setting based on progression-free
10 survival. And in the first-line setting, we agree
11 with CDER that a large magnitude of PFS benefit
12 with no impairment to overall survival is clinical
13 benefit.
14 Let's return to the biomarker component of
15 the confirmatory study. First, let's review the
16 analysis of plasma markers in AVADO. Biomarkers
17 were assessed in an optional sub-study with
18 separate patient consent. Fifty-four percent of
19 patients had a baseline plasma sample, and,
20 importantly, patient prognostic factors did not
21 differ between patients who did and did not have
22 samples.

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1 Plasma markers were selected based on their
2 role in angiogenesis and metastasis. For the
3 primary analysis, the marker cutoff was
4 prespecified to be the median value. Additional
5 analyses were performed on marker quartiles to
6 further explore the relationship between VEGF-A
7 levels and efficacy. Standard Cox regression
8 methods were used to control for baseline
9 characteristics.
10 What we found in AVADO was that high levels
11 of plasma VEGF-A were predictive of a larger
12 benefit of Avastin with a hazard ratio of .87 in
13 the VEGF low group and .49 in the VEGF high group.
14 The interaction test was borderline significant at
15 .08. To explore the cutoff value by quartiles, we
16 looked at the results and saw the benefit increased
17 from .87 in the lowest quartile up to .40 in the
18 highest quartile.
19 Other findings were that high VEGF-A was
20 strongly prognostic for poor outcome in both PFS
21 and OS, and this was unrelated to other baseline
22 characteristics. High VEGF-A was not found to be

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1 predictive for overall survival in AVADO, although
2 this analysis has the caveat that there were a
3 smaller number of overall survival events in the
4 biomarker sub-study.
5 Next steps include development of a
6 commercially plasma VEGF-A assay and prospective
7 validation within the confirmatory study. We
8 continue to pursue the plasma VEGF-A hypothesis in
9 other tumor types. To date, we have supporting
10 data in some tumor types but not in others.
11 So to summarize the confirmatory study, we
12 have designed a study of Avastin plus paclitaxel
13 specifically designed to confirm the substantial
14 magnitude of benefit seen in E2100 in all patients.
15 Current enrollment projections indicate that this
16 study is feasible, both by taking advantage of
17 global enrollment and by investigator interest in
18 the biomarker question.
19 We are planning an interim analysis of PFS,
20 which could trigger an early voluntary withdrawal
21 of the accelerated approval by Genentech if the
22 magnitude of benefit of E2100 is not likely to be

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1 confirmed by the futility boundary.
2 We met with CDER in February to discuss the
3 design, and their feedback was very clear. CDER
4 said that confirming the magnitude of PFS seen in
5 E2100 with no detrimental in OS would support full
6 approval of Avastin in metastatic breast cancer.
7 This study also provides the opportunity to
8 validate the emerging hypothesis that high VEGF-A
9 is predictive of larger clinical benefit, an area
10 in which both FDA and ODAC have expressed interest.
11 My overall conclusions are shown here.
12 First, we are confident in the strong and
13 meaningful PFS benefits in E2100. The issues
14 raised by CDER in 2001 and again more recently were
15 reviewed carefully. We found that these concerns
16 were not unique to E2100. They are seen in the
17 pivotal studies of approved breast cancer
18 medications, and there was no evidence of bias.
19 Second, AVADO and RIBBON 1 do not invalidate
20 E2100. They were well-conducted. They were
21 completed promptly. They met their primary
22 endpoints with high statistical confidence. They

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1 did use a different chemotherapy backbone and
2 schedule than E2100.
3 But what has changed and why we are here
4 today is that now we have clarity from CDER on what
5 is needed to convert Avastin to full approval, by
6 confirming the magnitude of benefit from E2100.
7 With that change, it's Genentech's position that
8 the proper course forward is to perform a
9 confirmatory study with weekly paclitaxel. We have
10 agreement with CDER on the design of the study and
11 what it must show.
12 Thank you for your attention, and now I
13 invite Dr. Joyce O'Shaughnessy to the podium.
14 DR. O'SHAUGHNESSY: Dr. Midthun, ODAC and
15 CDER colleagues, ladies and gentlemen, I appreciate
16 the opportunity to share with you my perspectives
17 on the clinical utility of Avastin-paclitaxel as
18 first-line treatment for metastatic breast cancer.
19 I hold the Celebrating Women Endowed Chair
20 in Breast Cancer Research at Baylor University
21 Medical Center, and I am co-chair of the U.S.
22 Oncology Breast Cancer Research Program. In

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1 addition to my involvement in breast cancer
2 clinical research, I am a practicing medical
3 oncologist who is focused solely on the care of
4 breast cancer patients.
5 I am here with Genentech, who has paid for
6 my time and travel to this meeting. I have been
7 involved in developing and enrolling patients onto
8 Avastin breast cancer clinical trials since 2000.
9 I have come to speak to you today because, as a
10 breast cancer specialist, I am very aware of where
11 we still have gaping unmet medical needs that cause
12 significant suffering. But first, it is important
13 to understand that there are three main types of
14 HER2-negative metastatic breast cancer.
15 Slow-growing, indolent, estrogen-receptor
16 ER, positive breast cancer is often without
17 symptoms and is probably best treated not with a
18 combination but with sequential single-agent
19 chemotherapy when hormonal therapy is no longer
20 effective.
21 Aggressive ER-positive breast cancer often
22 causes debilitating bone pain or threatens liver or

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1 lung function.
2 Triple negative breast cancer is highly
3 symptomatic in most patients, has a median survival
4 of only 12 to 18 months, and few known effective
5 treatment options. Triple negative metastatic
6 breast cancer and aggressive ER-positive disease
7 are best treated with combination chemotherapy, or
8 Avastin-paclitaxel.
9 In my practice, the Avastin-paclitaxel
10 combination plays an important role in alleviating
11 the symptoms that occur with aggressive metastatic
12 breast cancer. Just last week alone, having
13 carefully considered all of the available options,
14 I recommended to three patients who have metastatic
15 triple negative breast cancer and who are in need
16 of rapid relief from severe bone pain, chest wall
17 and arm pain, and liver pain that they begin
18 treatment with Avastin-paclitaxel.
19 As co-chair of the U.S. Oncology Breast
20 Cancer Committee, I oversee the development and
21 conduct of breast cancer clinical trials within the
22 U.S. oncology network. In this capacity, I have

<p style="text-align: right;">Page 81</p> <p>1 been involved in the evaluation of several new 2 agents and regimens that have helped shape the 3 current standards of care for patients with early 4 and metastatic breast cancer, some of which I have 5 listed on this slide.</p> <p>6 I have also had a longstanding interest in 7 clinical trial endpoints for metastatic breast 8 cancer. Twenty years ago, I served as the 9 coordinator for a joint FDA and NCI working group 10 that published a commentary on demonstrating safety 11 and efficacy of investigational anti-cancer agents 12 in clinical trials. Twelve years after this 13 publication, a follow-up report stated that between 14 1990 and 2002, endpoints other than survival were 15 the approval basis for 68 percent of regular 16 approvals and for 100 percent of applications 17 granted accelerated approval by FDA.</p> <p>18 So what are key treatment goals and 19 endpoints? The accepted treatment goals for 20 metastatic breast cancer and to prolong and/or to 21 improve or preserve patients' overall functioning 22 and performance status by decreasing or preventing</p>	<p style="text-align: right;">Page 83</p> <p>1 three-month improvement in PFS and the 12- to 2 15 percent improvement in response rates seen with 3 these approved combination chemotherapy regimens 4 used in clinical practice as first-line treatment.</p> <p>5 Importantly, and my main message to you as a 6 practicing clinician, is that the higher response 7 rate and longer progression-free survival do 8 provide meaningful clinical benefit to patients 9 with rapidly progressive symptomatic or heavily 10 tumor-burdened metastatic breast cancer.</p> <p>11 Triple negative breast cancer is an 12 especially grave form of metastatic breast cancer, 13 and very few clinical trials have shown defined 14 treatment benefit in this group. Looking at the 15 triple negative data from E2100, there is a 16 21 percent increase in response rate and a five- 17 month improvement in progression-free survival with 18 Avastin-paclitaxel.</p> <p>19 There is also a trend towards improved 20 survival in this group. On the right, the pooled 21 data from all the first-line Avastin trials in my 22 mind corroborate a definite clinical benefit in</p>
<p style="text-align: right;">Page 82</p> <p>1 tumor-related symptoms for as long as possible with 2 the least possible treatment-related toxicity in 3 clinical trials and in the clinic. The goals of 4 decreasing or preventing tumor-related symptoms and 5 prolonging disease control are accomplished by 6 improving response rates and progression-free 7 survival. A very important aspect of managing 8 metastatic breast cancer is to alleviate and 9 prevent the symptoms that impair function with the 10 least possible treatment-related toxicity.</p> <p>11 This slide shows the key efficacy results 12 for the four most commonly used combination 13 therapies for aggressive metastatic breast 14 cancer: Avastin-paclitaxel, gemcitabine- 15 paclitaxel, docetaxel-capecitabine, and 16 ixabepilone-capecitabine.</p> <p>17 Avastin-paclitaxel provides a higher rate 18 and a longer duration of disease control, as is 19 seen by the improved response rate and the longer 20 progression-free survival in E2100. The magnitude 21 of the PFS and response rate benefit with Avastin- 22 paclitaxel compares favorably to the two to</p>	<p style="text-align: right;">Page 84</p> <p>1 this triple negative population that has great 2 unmet need.</p> <p>3 Importantly, in my experience, Avastin- 4 paclitaxel is a well-tolerated combination regimen. 5 In contrast to combination chemotherapy, the 6 toxicities associated with Avastin-paclitaxel are 7 generally not treatment-limiting. Oncologists 8 must, of course, consider a patient's underlying 9 risk for developing the uncommon but serious 10 toxicities that can occur with Avastin-paclitaxel 11 in order to avoid a potentially serious side 12 effect.</p> <p>13 As we heard from several of the women who 14 testified yesterday, the most common Avastin- 15 related toxicity, hypertension, and the less common 16 toxicity, proteinuria, are typically without 17 symptoms, manageable, and, in my experience, 18 reversible. This tolerability allows patients to 19 have the sustained progression-free survival 20 benefit that can be achieved by combining two 21 agents. This is difficult to accomplish with a 22 combination of two chemotherapy drugs due to the</p>

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1 need for dose reductions and the eventual need to
2 stop one or both agents due to cumulative toxicity.
3 Avastin and paclitaxel is compatible with a
4 good quality of life for my patients. To
5 illustrate this point, shown here is a summary of
6 the toxicities that can lead to dose reductions for
7 the main four combination regimens. I have bolded
8 for you the toxicities that had double-digit
9 increases when the combination regimen was compared
10 with single-agent taxane or capecitabine.
11 The three combination chemotherapy regimens
12 lead to increases in neutropenia, which is a
13 lowering of the white blood cell count; neuropathy,
14 which is numbness and tingling in the hands and
15 feet; hand-foot syndrome, which is redness and pain
16 in the hands and feet; and stomatitis, which causes
17 mouth sores. These toxicities are in contrast to
18 those seen on the left with Avastin-paclitaxel,
19 which generally don't limit the delivery of
20 therapy.
21 In conclusion, Avastin-paclitaxel is an
22 important treatment option in my practice. The

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1 longer progression-free survival and higher
2 response rate do provide meaningful clinical
3 benefit to my patients with symptomatic or rapidly
4 advancing disease who require combination therapy.
5 The toxicities associated with Avastin-paclitaxel
6 are generally not treatment-limiting, which allows
7 for the delivery of sustained combination therapy.
8 Loss of access to Avastin-paclitaxel would
9 most acutely impact metastatic triple negative
10 patients who have few effective treatment options,
11 as well as patients with aggressive symptomatic
12 ER-positive breast cancer. It is on behalf of the
13 women in my practice who have aggressive metastatic
14 breast cancer and those who I unfortunately will
15 meet in the future who are best treated with
16 tolerable and effective combination therapy that I
17 have come to speak to you today.
18 As you will hear in a few minutes as well
19 from Dr. Barron, I call on the FDA to work with the
20 sponsor to keep Avastin-paclitaxel available as an
21 approved option, even if it means limiting the
22 indication to patients with metastatic triple

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1 negative and aggressive ER-positive breast cancer
2 whom their oncologists believe need combination
3 therapy while the confirmatory trial is being done.
4 Thank you very much for allowing me to share
5 my experience with you, and I would now like to
6 introduce Michael Labson from Covington & Burling.
7 MR. LABSON: My focus today as an attorney
8 specializing in food and drug regulation will be on
9 why the legal provisions governing accelerated
10 approval call for retaining Avastin as an approved
11 treatment option. I will review the statute,
12 regulations, prior guidance from CDER, and the
13 Department of Health and Human Services. I will
14 also do a fuller walk-through of the regulatory
15 history of Avastin because it explains why we are
16 here and why we disagree with the statement
17 yesterday that we are seeking multiple bites at the
18 apple.
19 This slide shows the key legal provisions
20 that govern accelerated approval. The overarching
21 purpose, as set out in the statute, the reason we
22 have accelerated approval, is to facilitate the

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1 availability of treatments in areas of unmet
2 medical need. Metastatic breast cancer is an area
3 of high unmet medical need.
4 The approval provision states that FDA may
5 approve a medicine based upon an effect on a
6 clinical endpoint or on a surrogate endpoint
7 reasonably likely to predict clinical benefit.
8 FDA's regulations specify further that the clinical
9 endpoint may be an effect other than survival or
10 irreversible morbidity where there remain
11 unanswered questions about a medicine's effect on
12 ultimate outcomes.
13 Avastin's approval for breast cancer is
14 based on progression-free survival, as you heard
15 yesterday, an endpoint CDER agrees is meaningful in
16 this setting without a showing of overall survival
17 or improvement in quality of life.
18 For withdrawal, the law states that FDA may
19 withdraw approval if a post-approval study fails to
20 verify clinical benefit or other evidence
21 demonstrates that a treatment is not safe or
22 effective. CDER's view on withdrawal is that

<p style="text-align: right;">Page 89</p> <p>1 Avastin had its chance. We had the chance to 2 submit post-approval studies to confirm benefit, 3 and did not make that showing. 4 That rigid approach is not required under 5 the law, and it is not consistent with the law's 6 purposes, to provide access to a medicine that 7 addresses serious unmet medical need where there is 8 a meaningful showing of benefit but questions 9 remaining regarding the magnitude of that benefit. 10 The data and the regulatory history for 11 Avastin call for the exercise of the flexibility 12 that the law provides to maintain accelerated 13 approval. Let's look first at the regulatory 14 option CDER had for Avastin in 2008. At that time, 15 CDER had data from E2100, top-line AVADO data, 16 mature PFS results, and immature OS data. CDER 17 also had later-line capecitabine data from the 18 2119g study. 19 After heavily vetting the E2100 study, CDER 20 concluded the data were reliable and supported 21 approval. In particular, CDER accepted PFS as a 22 meaningful endpoint, accepted Avastin's safety</p>	<p style="text-align: right;">Page 91</p> <p>1 refute the substantial effect on PFS for Avastin 2 with paclitaxel from E2100? 3 One view is that the data on Avastin with 4 paclitaxel stand distinct and benefit is confirmed. 5 That is the view of the European Medicines Agency, 6 numerous other health authorities, and the National 7 Comprehensive Cancer Network. Until 2010, 8 Genentech also thought that benefit was confirmed 9 under the standard set by CDER based on the 10 positive showing in AVADO and RIBBON 1. I will 11 come back to this point further in a few minutes. 12 CDER's view is at the other extreme, that 13 although the studies showed a robust effect and 14 involved different chemotherapy agents than E2100, 15 the results negate the showing of benefit from 16 E2100. That view leads to withdrawal. Indeed, we 17 heard yesterday that CDER has not even considered 18 any other options. 19 But there is a middle ground, drawing on the 20 discretion CDER acknowledged yesterday. Based on 21 the showing of benefit, if there are open questions 22 about the nature of Avastin's effect in metastatic</p>
<p style="text-align: right;">Page 90</p> <p>1 profile, and determined that Avastin provided 2 clinical benefit with favorable benefit-risk. 3 CDER had three regulatory options: full 4 approval, accelerated approval, or no approval. 5 And as CDER has explained and the review documents 6 show, CDER utilized accelerated approval to address 7 CDER's uncertainty about the scopes of Avastin's 8 effects. The accelerated approval provisions 9 worked in a flexible manner, as the law intends, to 10 provide a treatment option to patients with 11 significant unmet medical need and with post- 12 approval studies to address the open questions that 13 existed at that time. 14 Today we see the additional data, the mature 15 OS data for AVADO and data from RIBBON 1. There 16 are also the data from RIBBON-2 showing a PFS 17 effect outside the first-line setting. AVADO and 18 RIBBON 1 met their PFS endpoints, but with a lesser 19 magnitude of effect for Avastin with non-paclitaxel 20 chemotherapy. Safety is unchanged, as you heard 21 from CDER yesterday. The question is, do these 22 data on Avastin with other chemotherapy agents</p>	<p style="text-align: right;">Page 92</p> <p>1 breast cancer, and particularly its effect with 2 paclitaxel, the appropriate course is to retain 3 accelerated approval subject to a new study 4 designed directly to confirm the magnitude of 5 benefit for Avastin with paclitaxel. This is the 6 course Genentech has proposed. 7 The law provides this flexibility, and this 8 middle course best meets the purposes of 9 accelerated approval, to facilitate needed 10 treatment options for a severe disease pending 11 further study to confirm the level of benefit 12 already shown in E2100. CDER and HHS have both 13 previously emphasized this precise point. 14 At the 2003 ODAC on the accelerated approval 15 program, Dr. Robert Temple explained, "When a drug 16 has proved active, you don't lightly remove it 17 because a trial failed. You try to do other 18 studies. You think about why the studies failed." 19 At the same ODAC, Dr. Pazdur emphasized that 20 the regulations provide flexibility on withdrawal 21 decisions, and that withdrawal may not be 22 appropriate where a confirmatory study does not</p>

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1 confirm clinical benefit. As Dr. Pazdur explained,
2 “The withdrawal provision in the regulation gives
3 us judgment so we don’t to have a reflex situation;
4 you fail, therefore you must come off.”
5 Here CDER agrees that the post-approval
6 studies met their endpoints and show that Avastin
7 is active in metastatic breast cancer with no new
8 safety new signals. On these facts, Dr. Temple’s
9 and Dr. Pazdur’s cautions to exercise regulatory
10 judgment and not to move automatically to
11 withdrawal are particularly on point.
12 CDER’s comments from the 2003 ODAC have been
13 echoed by the Department of Health and Human
14 Services, HHS, FDA’s parent agency, also
15 emphasizing that FDA should proceed with caution in
16 considering withdrawals of accelerated approval.
17 In 2009, in official comments to the Government
18 Accountability Office, HHS explained, “When trials
19 do not appear to confirm clinical benefit, FDA must
20 carefully assess each case and the consequences of
21 all regulatory options, including their potential
22 impact on patients.”

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1 HHS further stated, “Failure to confirm
2 clinical benefit in a completed trial may reflect
3 unforeseen limitations in trial design rather than
4 clear evidence of lack of effectiveness.” Here the
5 post-approval trial showed effectiveness in a
6 disease with extremely limited treatment options.
7 The impact on patients from withdrawal would be
8 great.
9 The unforeseen limitation was the difference
10 in magnitude by chemotherapy partner, particularly
11 when focusing heavily on the medians, and
12 relatedly, CDER’s evolving emphasis on replicating
13 the magnitude of improvement in median PFS from
14 E2100.
15 Because accelerated approval is intended to
16 keep a medicine available where there is a
17 meaningful showing of benefit but some remaining
18 uncertainty, we strongly disagree with CDER’s
19 assertion that allowing a new confirmatory study
20 here undermines the accelerated approval program.
21 As the comments from HHS, Dr. Temple, and
22 Dr. Pazdur caution, a rigid approach to withdrawal

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1 does not best serve patients.
2 Here the regulatory history of Avastin shows
3 that one of the unforeseen limitations of AVADO and
4 RIBBON 1 is that the trials would be expected not
5 just to show a PFS benefit but to replicate the
6 5.5-month change in median PFS from E2100. That is
7 not the guidance Genentech received when
8 identifying AVADO and RIBBON 1 as appropriate
9 confirmatory trials.
10 In 2008, when CDER granted accelerated
11 approval, it understood that AVADO and RIBBON 1
12 would not replicate the PFS results from E2100.
13 This slide shows the office director’s review memo
14 supporting approval in 2008. As indicated, CDER
15 specifically requested the preliminary results of
16 AVADO before taking regulatory action.
17 The definitive PFS data were available, and
18 the office director noted that there was an
19 improvement in PFS based on data for the standard
20 Avastin dose, showing a hazard ratio for PFS of
21 0.64, a 36 percent reduction in the risk of disease
22 progression or death, an improvement in median PFS

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1 of 0.8 months, and an 18.6 percent improvement in
2 objective response rate. There is no mention of
3 overall survival or an overall survival trend.
4 CDER thus knew, in approving Avastin for
5 metastatic breast cancer and accepting AVADO as a
6 post-approval trial, that AVADO would show benefit,
7 but would not replicate the magnitude of
8 benefit -- the magnitude of median PFS effect from
9 E2100. And we heard yesterday that CDER never
10 communicated to Genentech that AVADO was not
11 adequate to confirm benefit.
12 For RIBBON 1, in a January 10, 2006 meeting,
13 CDER acknowledged that, “The treatment effect will
14 vary according to the chemotherapy regimen used.
15 The test will be whether there is a treatment
16 effect for each chemotherapy pairing.”
17 CDER recognized that the different
18 chemotherapy regimens will yield different effects.
19 CDER accepted the study design with target hazard
20 ratios of 0.7 and 0.75 for the two study arms, and
21 did not say that RIBBON 1 would only be considered
22 to show clinical benefit with a level of effect on

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1 median PFS near 5.5 months.
2 Here's the key Type B meeting from
3 February 2009, before the AVADO and RIBBON 1
4 supplements are submitted. In advance of that
5 meeting, Genentech provided CDER the top-line AVADO
6 and RIBBON 1 results. With this information in
7 hand, CDER stated in official meeting minutes, "FDA
8 confirmed that the basis for conversion to full
9 approval will be demonstrated improvement in
10 progression-free survival and evidence that
11 survival is not impaired."
12 There is no statement that AVADO and
13 RIBBON 1 failed to confirm benefit, even though
14 CDER had received the median PFS results from the
15 studies. There is also no reference to the need
16 for Genentech to replicate a change in median PFS
17 near 5.5 months, as in E2100, to confirm benefit.
18 It is not until the July 2010 ODAC and the
19 NOH that CDER states that the magnitude of median
20 PFS change from E2100 must be replicated or there
21 must be an effect on overall survival. But
22 Genentech did not have this guidance when

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1 identifying AVADO and RIBBON 1 as confirmatory
2 trials. In fact, we heard yesterday that CDER felt
3 it was unable at that time to give specific
4 guidance on the required magnitude of benefit.
5 This explains where we now are. CDER's
6 thinking changed over time, and we thus have post-
7 approval studies that, in hindsight, are limited in
8 their designs to meet CDER's expectation of
9 reproducing the magnitude of median PFS benefit
10 from E2100.
11 This regulatory history shows that Genentech
12 is not trying to undermine the accelerated approval
13 program by gaining inappropriate multiple bites at
14 the apple. Rather, Genentech is trying to respond
15 to its understanding of CDER's evolving thinking on
16 how to establish clinical benefit for Avastin in
17 this setting.
18 Maintaining approval subject to a new study
19 is an opportunity to conduct a confirmatory trial
20 squarely addressed at confirming the magnitude of
21 benefit for Avastin with paclitaxel, with the
22 required showing for full approval now clearly

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1 established.
2 The need to consider the option of a new
3 study rather than withdrawal is especially great
4 under our facts. All of the first-line studies met
5 their agreed-upon PFS endpoints. The data from the
6 secondary endpoints also showed consistent effects.
7 The greatest effect we have is for Avastin with
8 paclitaxel, and CDER accepts it is robust and
9 clinically meaningful. CDER's open questions are
10 the magnitude of benefit and the role of the
11 chemotherapy partner. These questions can be
12 addressed through further study.
13 Safety. Safety is well-characterized and
14 presented in the approved prescribing information.
15 CDER agrees there are no new safety signals. And
16 as you have heard from Dr. Horning and
17 Dr. O'Shaughnessy, the overall safety profile is in
18 line with other treatment options.
19 Genentech completed the post-approval
20 studies with rigor and diligence. An unmet medical
21 need persists. In over three decades, looking at
22 non-hormonal HER2 status unspecified medicines, FDA

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1 has approved only one other treatment for first-
2 line metastatic breast cancer, Gemzar, with a
3 2.3 month improvement in disease progression, no
4 proven survival benefit, and toxicity. As you
5 heard yesterday, there are no MBC treatments
6 approved with labeling for quality of life, and no
7 survival benefit has been approved for first-line
8 treatments outside hormone-positive, HER2-positive
9 disease.
10 We are not aware of any other instance where
11 FDA has sought to withdraw accelerated approval on
12 such facts, and it is not the right outcome here.
13 Withdrawal would remove a therapeutic option with
14 demonstrated efficacy, and it would narrow the
15 viability of the accelerated approval pathway for
16 sponsors by establishing an inflexible approach to
17 the consideration of post-approval studies.
18 These facts provide the answers to the
19 issues the presiding officer has stated will be
20 presented in this proceeding. Issue 1 asks whether
21 AVADO and RIBBON 1 failed to verify clinical
22 benefit for Avastin with paclitaxel. The answer is

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1 no, because they showed a statistically significant
2 benefit and a robust effect seen especially in the
3 hazard ratios.
4 Issue 2(a) asks whether the totality of the
5 data show that Avastin with paclitaxel does not
6 provide benefit. No. The data show clear
7 effectiveness in the first-line setting,
8 particularly with paclitaxel.
9 Issue 2B asks whether the data fail to
10 establish safety and favorable benefit-risk. No.
11 The safety profile is well-characterized and has
12 not changed. It is a profile that CDER accepts
13 across a range of other approved indications for
14 Avastin. The most common adverse events are
15 generally manageable. Other serious adverse events
16 are rare.
17 Issue 3 asks, if the data have not confirmed
18 the safety and effectiveness for Avastin with
19 paclitaxel, should accelerated approval be
20 maintained subject to the conduct of an additional
21 study? The answer is yes. Maintaining Avastin as
22 an approved option is called for by law, supported

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1 by the data, and in the best interest of patients.
2 This final issue is in large measure the
3 fundamental question for these proceedings. The
4 EMA, other health authorities, the NCCN, and many
5 oncologists, patients, and cancer organizations, on
6 the same studies, have concluded that the data
7 validate that Avastin is a valuable treatment
8 options. Others are not convinced. But the issue
9 here is whether there should be a sweeping
10 regulatory action that withdraws Avastin as an
11 approved option for all in an area where the
12 options are already too few, or whether physicians
13 and patients should be left to make informed
14 individual decisions, with appropriate prescribing
15 information, while further work is done.
16 The law provides a path forward between the
17 two poles of full approval, as in Europe, or full
18 withdrawal, as CDER has proposed. Retain
19 accelerated approval and require a true
20 confirmatory trial designed to meet the
21 expectations CDER has now clearly set out.
22 Thank you for your attention. Dr. Hal

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1 Barron will now provide our concluding remarks.
2 DR. BARRON: Thank you very much.
3 Before we end, I want to make a couple of
4 comments on what we have heard over the past day
5 and a half and how we have come to see the issues
6 at hand. Hopefully this is helpful for you,
7 Dr. Midthun.
8 We have seen many slides with many, many
9 numbers; hazard ratios, response rates, confidence
10 intervals, p values, et cetera. But what we cannot
11 lose sight of, though, is the many women behind
12 these numbers.
13 We have heard moving testimonials from
14 numerous women who have described their enormous
15 hardship from being diagnosed with this devastating
16 and incurable disease, how grateful they are for
17 the simple pleasures in life, and how significant
18 their unmet need truly is.
19 In the subsequent presentation, CDER made it
20 clear that despite the fact that both confirmatory
21 studies demonstrated an improvement in the
22 prespecified primary endpoint of PFS and that there

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1 were no new safety signals observed, this isn't
2 enough to allow accelerated approval to be
3 maintained while we confirm the magnitude of
4 effects seen in E2100 and a subsequent study.
5 What became clear at the end of CDER's
6 presentation is why we have come to divergent
7 conclusions. CDER stated that the first-line
8 metastatic breast cancer indication does not
9 represent an unmet need. CDER even went further to
10 state that if these women did have an unmet need,
11 as do women in later stages of their disease, the
12 criteria for clinical benefit would have been "more
13 lenient."
14 We respectfully but strongly disagree.
15 These women have a significant unmet need and
16 deserve the option to be treated with Avastin in
17 combination with paclitaxel. This is the key issue
18 for Dr. Midthun and Dr. Hamburg to decide.
19 We are willing to work with the FDA, as
20 Dr. O'Shaughnessy alluded to, to find a solution,
21 such as a modified or restricted label. Our
22 primary objective is to preserve, in an appropriate

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1 manner, options for women with metastatic breast
 2 cancer.
 3 Thank you for your attention and for
 4 allowing us this opportunity to provide our
 5 perspective.
 6 DR. MIDTHUN: Thank you very much.
 7 We will now break for half an hour, and
 8 return at 10:30.
 9 (Whereupon, a recess was taken.)
 10 Questions by CDER
 11 DR. MIDTHUN: All right. We will now go to
 12 the next portion of our session, which will be the
 13 opportunity for the CDER panel to present questions
 14 to the Genentech presenters, and there will be one
 15 hour for that.
 16 MS. CARTWRIGHT: Thank you, and good
 17 morning. We'd like to begin with your proposed
 18 withdrawal standard.
 19 May I have slide 128, please?
 20 This is Genentech's proposed withdrawal
 21 standard. "Withdrawal is not appropriate unless
 22 the data establish that there is no longer a

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1 reasonable likelihood of clinical benefit, and no
 2 meaningful way to characterize the potential
 3 benefit further."
 4 Can you tell us of anyplace where FDA has
 5 stated the withdrawal standard in this way?
 6 MR. LABSON: Well, our point here is simply
 7 that where the data that you have from the original
 8 trials and the post-approval trials show a benefit
 9 but there's uncertainty, that the purpose of the
 10 accelerated approval law is met by keeping the
 11 medicine as a treatment option.
 12 That's sort of the fundamental purpose of
 13 the statute, and that still exists when you're
 14 looking at the data after the post-approval trials
 15 are confirmed. And that's consistent with the
 16 statements and interpretation we see from the 2003
 17 ODAC and from the HHS comments about needing to
 18 approach withdrawal carefully based on the
 19 particular facts at hand.
 20 MS. CARTWRIGHT: But that is not the
 21 withdrawal standard in the statute or the
 22 regulations?

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1 MR. LABSON: It is how we think the
 2 withdrawal -- what the withdrawal standard means
 3 and how it's interpreted. It provides that -- we
 4 agree that the withdrawal provisions, an important
 5 part of the scheme, and it provides that FDA may
 6 withdraw approval if post-approval trials don't
 7 confirm benefit. But that has to be judged based
 8 on the facts that you have and in light of the
 9 purposes of the law, to make treatments available
 10 in areas of unmet medical need.
 11 MS. CARTWRIGHT: Doesn't this standard
 12 actually shift the burden to FDA to prove that
 13 there is no longer a reasonable likelihood of
 14 clinical benefit, rather than placing the burden on
 15 the sponsor to establish that the product is safe
 16 and effective?
 17 MR. LABSON: No. We would agree the burden
 18 is to show that there's a benefit, with
 19 uncertainty. That's why you're still under
 20 accelerated approval and not regular approval.
 21 MS. CARTWRIGHT: You also stated in your May
 22 submission that if the confirmatory study fails to

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1 meet the standards CDER set in the February 2011
 2 Type B meeting, withdrawal could then be
 3 appropriately considered.
 4 What results of your proposed study would
 5 constitute a failure under your proposed withdrawal
 6 standard?
 7 DR. REIMANN: Yes. As you heard in our
 8 presentation, we are proposing an interim analysis
 9 of progression-free survival specifically for the
 10 purpose of regulatory futility. By that, I mean,
 11 if the results at that time indicate that it is
 12 unlikely that the magnitude of effect seen in E2100
 13 will be confirmed -- and will you please bring up
 14 the slide -- then we will propose -- sorry. I just
 15 want to get the slide up here. Let me talk you
 16 through the slide from the top.
 17 The purpose of the interim analysis is to
 18 rule out a large magnitude of PFS benefits similar
 19 to that seen in E2100, and we heard from Dr. Pazdur
 20 on this yesterday. It is important that the study
 21 would still continue to the final analysis, and
 22 that is because of the biomarker question. We

<p style="text-align: right;">Page 109</p> <p>1 don't want to inhibit the study from answering the 2 important biomarker question. But the interim 3 analysis results could trigger withdrawal based on 4 futility boundary. 5 We have not yet discussed this boundary with 6 FDA, and we think that's an important discussion. 7 When we met with FDA earlier this year to discuss 8 the confirmatory study, CDER didn't want to talk 9 about the ongoing accelerated approval, so we 10 haven't yet had that opportunity. We see this 11 futility boundary being based largely on the hazard 12 ratio, but also informed by the absolute benefit. 13 MS. CARTWRIGHT: But once you had this 14 interim analysis under your reading of the 15 regulations and the approach to withdrawal, how 16 many additional trials would you say would be 17 necessary before you would agree that you'd failed 18 to confirm benefit? 19 DR. REIMANN: This is the definitive 20 additional trial. 21 MS. CARTWRIGHT: So where your slide says 22 that it could lead to voluntary withdrawal, you're</p>	<p style="text-align: right;">Page 111</p> <p>1 our global CRO, and an initial questionnaire that 2 went out to the countries specific to this 3 protocol. The more detailed feasibility analysis 4 is currently ongoing and will deliver results in 5 early July. 6 This more detailed feasibility assessment is 7 looking at the standard of care in the different 8 countries, the ability of the study sites to follow 9 the protocol as specified, and, of course, their 10 interest in the protocol. We also need to make 11 sure that there is a proper handling of biological 12 specimens by local laboratories to make sure the 13 protocol is conducted as in the high level protocol 14 summary we discussed with FDA early this year. 15 So in short, we will have the updated 16 feasibility in early July to inform our discussions 17 with CDER coming this fall. 18 DR. JENKINS: Are you planning to conduct 19 this confirmatory trial in countries where the 20 Avastin plus paclitaxel indication is approved by 21 the regulatory agency in that country? 22 DR. REIMANN: We have approached</p>
<p style="text-align: right;">Page 110</p> <p>1 saying that it would. This would be the definitive 2 trial? 3 DR. REIMANN: I think CDER appreciates that 4 this would also be a discussion between CDER and 5 the company because it could be a possibility that 6 the different measures of magnitude do not entirely 7 agree at the boundary, and the Data Monitoring 8 Committee could have opinions on this matter as 9 well. 10 MS. CARTWRIGHT: Thank you. Dr. Jenkins is 11 going to ask you some questions now about the 12 actual proposed study. 13 DR. JENKINS: You mentioned in your 14 presentation that you're still conducting 15 feasibility analyses for this trial. Can you share 16 more information about that feasibility analysis as 17 far as how long you think it's going to take to 18 enroll this trial and when you expect to submit the 19 final study report for this trial? 20 DR. REIMANN: Yes. The preliminary 21 feasibility analysis has already been performed. 22 That was based on our prior enrollment experience,</p>	<p style="text-align: right;">Page 112</p> <p>1 approximately 50 countries for participation in the 2 study. Some of the countries, many of the 3 countries, have Avastin plus paclitaxel approved. 4 But I think here it's important to distinguish 5 regulatory approval from access to patients. In 6 many cases, the regional health authorities of the 7 state health authorities do not provide access to 8 patients. And so we believe this will be a very 9 attractive study in many locations where the trial 10 is being proposed, even in the United Kingdom. 11 DR. JENKINS: Do you plan to conduct the 12 study in the United States? 13 DR. REIMANN: We will have study sites in 14 the United States. Based on preliminary 15 feasibility, we believe the study will 16 predominately be enrolled outside of the United 17 States. 18 DR. JENKINS: Okay. Under your proposal, 19 the indication for paclitaxel would remain in the 20 label under accelerated approval. So I'm 21 wondering, in your feasibility assessment, you made 22 the point this morning in your presentation that</p>

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1 Genentech stands behind the view that the
2 progression-free survival benefit is 5.5 months,
3 that the 1-year survival benefit is a 7 percent
4 improvement, and that the two-year survival benefit
5 is a 4 percent improvement over paclitaxel alone.
6 So I'm wondering if your feasibility
7 assessment has included the likelihood of enrolling
8 patients in this study in the United States or
9 other countries where the indication is approved on
10 the label. We've heard in the past that patients
11 are reluctant to agree to be randomized to not
12 receive what's an approved treatment for their
13 serious and life-threatening condition. So if this
14 indication remains in the label, can you help me
15 understand the feasibility of conducting this trial
16 in those countries?
17 DR. REIMANN: I think it's obvious to
18 everybody at hand that we have this very public
19 hearing today, and there is a lot of dispute about
20 the data with FDA. But I'd like to ask Dr. Horning
21 to comment.
22 DR. HORNING: Well, I would concur with what

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1 Dr. Reimann just said, which is that there is
2 scientific debate over the interpretation of the
3 data, and there are varied opinions of physicians
4 and patients, as we heard yesterday. And we feel
5 that there will be a proportion of such patients
6 and physicians in the United States who are
7 currently at equipoise, or near equipoise, where
8 there will be interest in participating in such a
9 study. We also believe that the biomarker
10 component raises the scientific interest of the
11 study, and the interest of investigators as well as
12 patients.
13 DR. JENKINS: Can you share more details
14 about how you are planning the study? What effect
15 are you planning to confirm with your analysis? So
16 what's your planned analysis of this trial going to
17 look like, in your -- what will a win look like,
18 essentially, in your statistical analysis plan?
19 DR. REIMANN: I think we have to distinguish
20 win from the protocol versus win with the FDA. And
21 we heard, in fact, two different answers from CDER
22 yesterday on what the study would need to show. We

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1 heard a certain magnitude of median PFS or an
2 improvement in hazard ratio; and then we heard a
3 certain improvement in median PFS and an
4 improvement in hazard ratio. These two things are
5 quite different when sponsors consider the design
6 of confirmatory study.
7 We believe in providing a well-conducted
8 study with substantial evidence that will enable
9 that decision to happen, and we realize that will
10 be a discussion with CDER for the withdrawal. But
11 we are committed to get the study started as soon
12 as possible and to get data as soon as possible.
13 And we anticipate the interim analysis will be
14 conducted 3 and a half years after this coming Q1.
15 DR. JENKINS: Okay. I think we clarified
16 yesterday in our presentation that our focus has
17 been heavily driven by the magnitude of the median
18 difference in progression-free survival. And I
19 think we clarified that yesterday afternoon, that
20 Dr. Pazdur misspoke when he said the median or the
21 hazard ratio.
22 So are you planning -- do you expect this

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1 trial will show a median difference in progression-
2 free survival of the magnitude seen in E2100, which
3 was approximately 5 and a half months? Is that
4 what you're expecting to see?
5 DR. REIMANN: Yes. I think I would like to
6 clarify, though, what we heard at the end of CDER's
7 presentation yesterday, if I heard correctly in
8 your redirect, that CDER thinks we should confirm
9 exactly the median benefit and exactly the hazard
10 ratio. And I think it's important here that we
11 recognize that all clinical studies are conducted
12 with variability.
13 So if truth in the new study is 5.5 months,
14 then there's a 50 percent chance, just by
15 variability alone, of being less than 5.5 months,
16 and there's a 50 percent chance of it being greater
17 than 5.5 months. If we then also have to exactly
18 match a hazard ratio, you have a 50 percent chance
19 of it being less and 50 percent chance of it being
20 more.
21 So I think we need to get better clarity
22 from what the agency needs as far as the exact

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1 showing of benefit.
2 DR. JENKINS: But your expectation going in
3 is that you will replicate the 5 and a half month
4 progression-free survival seen in E2100?
5 DR. REIMANN: Yes, definitely. We are very
6 confident in the substantial benefit seen in E2100.
7 And what I personally expect to see is substantial
8 improvement in objective response, in progression-
9 free survival and 1-year survival. I think it's an
10 interesting fact that if we do a study of this
11 size, you would actually be powered to see a 1-year
12 survival benefit of approximately 6 percent.
13 I know that's not the discussion today, but
14 we believe we've designed a study that will provide
15 substantial evidence to enable a regulatory
16 decision. And the inclusion of the interim
17 analysis will enable that to happen sooner.
18 DR. JENKINS: I'd like to go back to that
19 interim analysis. Can you provide more detail
20 about the criteria for futility that you plan to
21 propose for the interim analysis? The slide you
22 projected was very vague on what the actual

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1 criteria would be. So where would Genentech see
2 futility in confirming the benefit in that interim
3 analysis that would lead you to voluntarily
4 withdraw this indication?
5 DR. REIMANN: Well, clearly that's a
6 discussion we need to have with CDER, and we
7 haven't had that discussion yet. I would envision
8 the futility boundary to be primarily based on a
9 hazard ratio, which I believe has superior
10 statistical properties for variability, but also be
11 informed by the absolute benefit. That includes
12 the median benefit, but also early benefits and
13 later benefits.
14 I think you can appreciate that if the
15 futility boundary is too loose, then we would
16 terminate a study early that actually would
17 replicate the management of benefit in E2100. So I
18 think it's a matter of us looking at the numbers
19 and sitting down together and working on it with a
20 boundary that we can both feel comfortable with.
21 DR. JENKINS: And you can't share your
22 proposal at today's meeting?

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1 DR. REIMANN: Actually, we wanted to be
2 informed by FDA's discussion of the magnitude of
3 benefit that had to be demonstrated to inform our
4 proposal.
5 DR. JENKINS: Thank you.
6 MS. CARTWRIGHT: You made some comments that
7 CDER has been inconsistent with regard to magnitude.
8 So we'd just like to go through a little bit of the
9 regulatory history on that point.
10 Would you agree that on October 28, 2004,
11 CDER told Genentech on a telephone conference that
12 approval based on PFS would depend on the overall
13 results and magnitude of PFS?
14 MR. LABSON: The issue isn't whether CDER
15 said that magnitude would be considered, which I
16 think is pretty straightforward. The point is that
17 CDER never communicated that the standard would be
18 a showing of median PFS of 5.5 months. And you can
19 see that in the regulatory history; for example,
20 having the AVADO results at the time that CDER
21 accepted AVADO as a confirmatory trial and knowing
22 that the median PFS, based on the data they had in

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1 hand, was 0.8 months, although the hazard ratio was
2 more in line with E2100.
3 MS. CARTWRIGHT: Well, speaking of the AVADO
4 results, did CDER ever tell Genentech that those
5 top-line AVADO results, which were communicated in
6 just a couple of slides, would confirm clinical
7 benefit for Avastin?
8 MR. LABSON: The key point is CDER accepted
9 AVADO as a confirmatory trial, knowing what the
10 data were.
11 MS. CARTWRIGHT: Well, at that time, wasn't
12 CDER also presented with results that indicated
13 there was a trend in overall survival in that
14 top-line data?
15 DR. HORNING: Just to clarify, CDER
16 requested and Genentech provided more than just a
17 couple of slides. There were actually 22 slides
18 that provided details of the clinical trial and the
19 results.
20 At that time, the results that were
21 available that you could hang your hat on, so to
22 speak, were the response rates, which were called

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1 out in the slides. And also the PFS, the
2 progression-free survival, at that time was mature,
3 with more than half the patients experiencing an
4 event. As we have spoken about earlier, at that
5 time, with the top-line definitive progression-free
6 survival results, the hazard ratio was 0.64 and the
7 median delta in PFS was 0.8 months.
8 There was also within that slide deck some
9 very preliminary survival data, with about
10 20 percent or less events at that point in time.
11 And it was called out in this office director's
12 memo that immature survival data had also been
13 viewed.
14 MS. CARTWRIGHT: And Genentech did direct
15 CDER's attention to that immature survival data
16 with the red circle that we saw on a slide
17 yesterday?
18 DR. HORNING: Within the slide deck, there
19 were several things that were called out, and the
20 overall survival data were called out at that time.
21 You can imagine that there would be interest in
22 overall survival because of the necessity for

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1 providing or demonstrating an improvement in
2 progression-free survival with no impairment in
3 overall survival.
4 So these preliminary data and the upper
5 bounds of the confidence interval would suggest
6 that it was very unlikely that you're going to see
7 an impairment in overall survival in AVADO based
8 upon the data that were provided at that point in
9 time.
10 MS. CARTWRIGHT: And is Genentech aware of
11 CDER making regulatory decisions based on top-line
12 data, be it two slides or 22 slides?
13 MR. LABSON: Well, we have Dr. Pazdur's
14 review memo from that time that said that CDER
15 specifically requested the AVADO data before making
16 regulatory action. Understand that CDER didn't
17 review the full data set, but I think he also
18 explained yesterday that he wanted to be sure, that
19 CDER wanted to be sure, before approving that it
20 wasn't going out on a limb where there would be a
21 failed study.
22 So I think the assessment wasn't a full

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1 review of the data, but saw the data to make the
2 conclusion that AVADO was not a failed study but a
3 study that showed benefit for Avastin in metastatic
4 breast cancer.
5 MS. CARTWRIGHT: Right. And I think
6 Dr. Pazdur also explained that was essential
7 because we did have a failed study in this case
8 with AB2119g. So thank you.
9 So talking about sort of the initial
10 approval in 2008, we'd like to just ask a couple of
11 questions about the ODAC meeting where the E2100
12 results were discussed. And if I could have slide
13 138.
14 This is a quote from Dr. Schenkein from
15 Genentech, and he said at that time, "The data
16 demonstrated robust and clinically meaningful PFS
17 treatment effect. In fact, it represents the
18 longest PFS seen to date with any treatment in this
19 setting. A PFS of this magnitude represents
20 clinical benefit for first-line treatment of
21 metastatic breast cancer patients."
22 So isn't it true that Genentech, in

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1 presenting the E2100 results, was really explaining
2 that the magnitude of 5.5 months was the key?
3 DR. HORNING: I think at the time that this
4 ODAC occurred and when the E2100 results were first
5 presented, there was tremendous excitement in the
6 community. I recall being in the audience at the
7 ASCO meeting when the results were first presented.
8 And indeed, the treatment effect that was seen in
9 E2100 at that time was unparalleled. And I believe
10 that you saw that in Dr. O'Shaughnessy's
11 presentation this morning.
12 So you've selected a statement that relates
13 to the meaningful PFS improvement as described in
14 medians; and the PFS improvement as described in
15 hazard ratio, with more than a 50 percent reduction
16 in the risk of disease progression or death, I
17 would submit is equally meaningful.
18 MS. CARTWRIGHT: And at that same meeting,
19 Genentech had a consultant, Dr. Winer present, and
20 he said, regarding the E2100 results, that for
21 progression-free survival to equal benefit, this
22 progression-free survival needs to be substantial

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1 in magnitude, it needs to be established with
2 confidence, and, ideally, it should be supported by
3 other measures of efficacy, by survival, by quality
4 of life, and by objective response rate. And that
5 also was a part of Genentech's presentation at that
6 ODAC meeting?
7 DR. HORNING: Yes. The response rate data
8 that we have called out today, the 28 percent
9 improvement in overall response rate, was a
10 secondary measure that would be consistent with
11 Dr. Winer's statement.
12 DR. JENKINS: I'd like to go to the
13 chemotherapy partner hypothesis that Genentech is
14 now proposing, that it's uniquely effective in
15 combination with paclitaxel.
16 Can you share with us, when did that
17 hypothesis really crystallize? As recently as
18 ODAC, Genentech was advocating for a broad labeled
19 indication for Avastin in combination with multiple
20 chemotherapy agents. So when did your hypothesis
21 that paclitaxel is the uniquely effective agent
22 crystallize in your mind?

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1 DR. HORNING: Well, I think from an
2 historical perspective, the initial introduction of
3 the hypothesis, if you will, that chemotherapy
4 matters was brought up at the ODAC meeting in 2007
5 that we were just discussing, that was brought up
6 by Dr. Kathy Miller from the University of Indiana.
7 And it was looking at the 2119 and the E2100
8 results and discussing potential reasons. I think
9 that also is very much in line with what you heard
10 from Mr. Labson about trying to understand trials
11 and looking deeper. So it had been ongoing for
12 some period of time.
13 When we were presenting our data in July of
14 2010, we felt at that time that we were presenting
15 the results of clinical trials that were positive
16 and had met the standard for a demonstrated
17 improvement in progression-free survival and no
18 impairment in overall survival.
19 As a consequence of the ODAC discussion and
20 our understanding of CDER's current thinking, we
21 more closely evaluated the overall study results in
22 this context. We see from the hazard ratios that

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1 there is an effect of Avastin in each of our
2 studies. We see that the effect is somewhat more
3 pronounced in E2100. And at that point in time, we
4 began to look at our data even more deeply with
5 regard to some of the differences in the
6 tolerability of paclitaxel in the clinic.
7 I will also say that during the ODAC
8 transcript, that I made references to this as well.
9 And if we could have the slide up. The statement
10 was made with regard to different types of
11 chemotherapy. And I had mentioned that there were
12 always differences in the tolerability of the
13 underlying chemotherapy, and that the time that
14 patients are actually on treatment and receiving
15 chemotherapy in combination with Avastin may be an
16 important parameter that we are speaking about
17 here.
18 DR. JENKINS: So at the time of the ODAC, is
19 it true that you were seeking approval for an
20 indication for use in combination with docetaxel as
21 well, based on the 0.8 months median survival in
22 AVADO?

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1 DR. BARRON: Let me just add one point to
2 the prior question. You used the term "uniquely."
3 I think you said "uniquely effective." And I think
4 the point of our presentation was to highlight the
5 fact that the hazard ratios and the benefit
6 observed in AVADO and RIBBON 1 was significant, and
7 we acknowledged that the treatment effect appeared
8 less in those two studies. But the benefit was
9 observed in those two studies. The primary
10 endpoint was significant. And so we are providing
11 a hypothesis as to why there might be greater
12 benefit with paclitaxel, but we wouldn't describe
13 it as uniquely effective such that the other
14 regimens were inactive.
15 DR. JENKINS: It goes to the question of
16 magnitude of PFS effect being clinically
17 meaningful. I think we have agreed and you have
18 agreed that the effect seen in E2100 is real and
19 the safety profile has not changed, and that would
20 be considered clinical benefit. At the time in
21 July, you appeared to believe that the effect seen
22 in combination with docetaxel was also evidence of

<p style="text-align: right;">Page 129</p> <p>1 clinical benefit, as low as 0.8 months of median 2 progression-free survival difference? 3 DR. HORNING: Well, our discussion in July 4 2010 at the ODAC was really to describe the 5 treatment effect and the ways that it can be viewed 6 scientifically. And when we look at the AVADO 7 study, the hazard ratio was 0.62, which is a 8 considerable treatment effect, certainly in line 9 with approved agents in metastatic breast cancer. 10 I think in the AVADO trial this is a case 11 where the median is underestimating the treatment 12 effect. Nonetheless, we do recognize that the 13 tolerability of docetaxel in combination with 14 Avastin is less good than with paclitaxel, and we 15 respect the judgment of those who've used the two 16 in combination as well as the decision that was 17 made in Europe. 18 DR. JENKINS: So you think the AVADO trial 19 is an underestimate of the effect, in combination 20 with docetaxel, but the E2100 is an accurate 21 estimate of the effect with paclitaxel? 22 DR. REIMANN: No. I don't think we would</p>	<p style="text-align: right;">Page 131</p> <p>1 the fact that Dr. Horning said that she thought 2 that the AVADO median PFS was an underestimate of 3 the true effect; and yet Genentech seems to think 4 that the E2100 results for paclitaxel combination 5 is the true effect at 5 and a half months. 6 I noted in your submission that you called 7 out that there's never been a trial in first-line 8 metastatic breast cancer that showed an effect of 9 5.5 months on median progression-free survival. 10 That's one of the issues that's in debate here, is 11 whether E2100 is an accurate representation of the 12 true effect or was an overestimate, an outlier, and 13 that the true effect is more in line with what 14 you've seen in the other trials, including what we 15 saw in Study 10, which Genentech submitted as part 16 of your submission and referenced us to. 17 So just highlighting that, I'm wondering how 18 it can be an underestimate in AVADO but an accurate 19 estimate in E2100. 20 DR. REIMANN: Okay. There are a lot of 21 questions there, so I'll address each one of them 22 in turn.</p>
<p style="text-align: right;">Page 130</p> <p>1 say that. I think the AVADO data, they are. They 2 showed a hazard ratio of .62, and the difference in 3 median PFS was .8 at the median. 4 If we could just put the slide up. I think 5 it's very misleading when we always describe 6 treatment effects in a time basis on medians 7 because this is an example, I think, of where the 8 medians are very close, showing .8 months. But 9 actually, there are many points on the curve where 10 the difference is bigger than .8 months. And this 11 actually was seen with a data update that I know 12 that FDA doesn't rely on. 13 But I think that we have other examples from 14 studies in oncology. I think, as an example, of 15 panitumumab in refractory colorectal cancer, which 16 did receive approval, where the medians are quite 17 notably almost on top of each other. And FDA used 18 some regulatory flexibility, describing the benefit 19 there as absolute improvement in PFS. 20 So I think this focus on medians is a 21 little -- there's too much of it right now. 22 DR. JENKINS: Yes. I was just picking up on</p>	<p style="text-align: right;">Page 132</p> <p>1 First, I don't think it's proper to 2 speculate about whether a study has an 3 underestimate or an overestimate. You have the 4 estimate. It has its confidence intervals. I 5 think that's the way statisticians describe data, 6 and that's the way we move forward in oncology. 7 With regard to E2100, if you could bring 8 this slide up, I spent half of my presentation 9 discussing E2100 in detail and why we are confident 10 in the treatment benefit in E2100, not just that 11 there was a benefit, but that it is of a 12 substantial magnitude. And I know that FDA has a 13 question about this, and that is what the purpose 14 of the confirmatory study is for, to definitively 15 answer this question once and for all. And so 16 we've already provided that protocol to the FDA, 17 and I think we have agreement on what that study 18 would need to show. 19 But I do want to respond to your question 20 about Study 10 because this did play a very large 21 part in CDER's presentation. There were quite a 22 few slides on this study, so I think it might be</p>

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1 helpful for the ODAC and for the presiding officer
 2 to know a little bit more about the study.
 3 If you could please bring up the study
 4 schema.
 5 The most important --
 6 DR. JENKINS: I'm sorry. I think we want to
 7 move on to other questions --
 8 DR. REIMANN: I'm sorry. I'm just trying to
 9 answer your question on Study 10.
 10 DR. JENKINS: -- not use our time during
 11 this section. We know about study 10. I think
 12 that's in the package. I'll turn to one of my
 13 colleagues for other questions.
 14 MS. CARTWRIGHT: We would like to ask a
 15 couple of other questions about your proposed
 16 study. You stated this morning that you will not
 17 complete the study for three and a half years after
 18 you begin enrollment, and you don't expect to begin
 19 accruing patients until next year.
 20 So do we correctly understand that your new
 21 study would not be completed, assuming everything
 22 goes perfectly, until approximately 2016?

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1 DR. REIMANN: You have the dates correct.
 2 Initial start of enrollment Q1, 2012. Interim
 3 analysis, three and a half years after that point.
 4 Final analysis, an additional year after that. We
 5 believe in the meantime, because of the substantial
 6 benefit that has been demonstrated in E2100, that
 7 it should be available to women with this
 8 indication.
 9 DR. JENKINS: So if I could just follow up
 10 on that. So you're saying three and a half years
 11 after first enrollment to interim analysis, and
 12 another year after that to final analysis? Is that
 13 correct?
 14 DR. REIMANN: Yes. That's exactly what I
 15 described in my presentation.
 16 DR. JENKINS: And from that until final
 17 study report submitted to FDA for review?
 18 DR. REIMANN: I think the important part
 19 about a voluntary withdrawal is that we wouldn't be
 20 anticipating a lengthy submission process of a
 21 preparation of a study report and a 10-month review
 22 period. I think this would be a very high level

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1 discussion between senior management at Genentech
 2 and senior management at CDER to come to a
 3 decision.
 4 DR. JENKINS: I'm just trying to understand
 5 when do you project you'll submit the final study
 6 report; three and a half years from first
 7 enrollment, another year, and then how much time.
 8 So are we talking essentially five years from first
 9 enrollment to get the final study report?
 10 DR. REIMANN: I think a study report would
 11 be submitted approximately four months after the
 12 database lock, as per standard. But as I just
 13 said, the ability to make a regulatory decision
 14 would be in advance of that.
 15 DR. BARRON: Let me just add one other point
 16 to that, that if we pass the futility mark, the
 17 probability is the trial is actually demonstrating
 18 what we expected to demonstrate, and therefore the
 19 delay is less of an issue. The reason we put the
 20 futility endpoint together is to ensure that if in
 21 fact the treatment effect is less, that we can
 22 inform the FDA and have withdrawal as quickly as

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1 possible without jeopardizing the quality of the
 2 trial.
 3 MS. CARTWRIGHT: So, again, just so we're
 4 clear, we're looking at approximately 2016/2017,
 5 and we could potentially be right back here having
 6 another proceeding to determine whether or not
 7 you've confirmed clinical benefit under your
 8 withdrawal rubric?
 9 DR. REIMANN: I think it's important to
 10 reflect that in the accelerated approval
 11 legislation -- if we could bring the slide
 12 up -- there are multiple examples that are in time
 13 frames similar to this. If we look at the top of
 14 the slide, we have products that had been subject
 15 to regulatory action that were 10.4, 11, 10 years
 16 from initial accelerated approval. We have found
 17 products who are currently under accelerated
 18 approval and have not yet converted that have more
 19 than six and a half or more than seven and a half
 20 years; and then products who have been converted to
 21 full approval, we see a number of products here in
 22 the range of 6 to 12 years.

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1 So, to be clear, this is not unprecedented,
2 this time frame.
3 MR. LABSON: The other key point is now we
4 have a clear statement from CDER about what will
5 confirm or not confirm, and Genentech did not have
6 that before. So now, with that standard clearly
7 set, Genentech has been able to put together a
8 proposal squarely aimed at that standard, and it
9 will give us a direct answer. It's different than
10 what we had before, where we didn't have clarity
11 about what CDER was looking for, and therefore have
12 studies that don't provide answers to the standard
13 now being imposed.
14 MS. CARTWRIGHT: We'll just need a moment.
15 [Pause.]
16 MS. CARTWRIGHT: So when you say that
17 Genentech was unclear on the standard, you were
18 clear that you were supposed to confirm the
19 magnitude of clinical benefit from E2100?
20 MR. LABSON: No. We're clear now. We
21 weren't clear then. There's also how is magnitude
22 being defined, hazard ratio focus or we're hearing

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1 this heavy focus on the medians at this point. But
2 I went through the regulatory history. I think it
3 shows there would have been no way for Genentech to
4 have understood that, where -- and, again, they
5 gave AVADO to CDER, the results, and it doesn't
6 match the E2100 results if you focus on the median.
7 So they did not know that before.
8 DR. BARRON: I think it's important to point
9 out that the AVADO and RIBBON trial were designed
10 with the intent to be able to observe a hazard
11 ratio between .7 and .75, and exceeding that
12 threshold with a positive trial can be described as
13 a magnitude of benefit.
14 What we're trying to explain is that we have
15 been acting on the belief that hazard ratios were
16 the best way to make cross-trial comparisons in
17 terms of magnitude of treatment effect. And we
18 believe that reflects the entire curve and more
19 data points, and it's the evolved focus on medians
20 that we're debating as new.
21 DR. JENKINS: I think we showed a slide
22 yesterday of an advertiser from Genentech that

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1 showed that the median progression-free survival
2 from E2100 was a major part of your advertising
3 campaign for that trial. So I'm curious; how can
4 you say that focus on the median is now new?
5 MR. LABSON: Respectfully, I don't think
6 that was a fair description of that one page out of
7 a visual aid, which presented information on both
8 the median and the hazard ratios with comparable
9 prominence. I would note, too, that was a piece
10 that was submitted in advance because we're under
11 accelerated approval, to DDMAC and it was okayed
12 for use.
13 DR. JENKINS: Well, I would note, I think
14 all of our slides yesterday where we presented the
15 results of the trials, we presented both the hazard
16 ratio and the median progression-free survival
17 numbers, as did that advertisement. So I'm just
18 curious where the idea ever came from that
19 confirmation of clinical benefit would only be
20 based on the hazard ratio from the trials and not
21 looking at both those pieces of information,
22 factoring it into the benefit-risk analysis.

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1 MR. LABSON: It's not that CDER wouldn't
2 have been expected to look at all the data,
3 including the medians. The point is that only a
4 median of 5.5 months would be considered clinically
5 meaningful. It just was never stated until the
6 2010 ODAC.
7 DR. JENKINS: So maybe one of the clinicians
8 on the panel, Dr. Barron or Dr. Horning, can help
9 me understand. If we're just looking at the hazard
10 ratio, how do I put that into a benefit-risk
11 assessment of looking at the toxicities of a drug,
12 and I have a .5 hazard ratio, as one of our
13 presenters noted yesterday, that could mean the
14 difference between 1 week and 2 weeks or 12 weeks
15 and 24 weeks, for example?
16 So how can I put a hazard ratio into
17 perspective without looking at the magnitude of the
18 median difference in progression-free survival?
19 DR. REIMANN: You can't. You need to look
20 both at hazard ratios and absolute benefits. But I
21 think it's important to look at absolute benefits
22 in time, not just at the median point, but it's the

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1 overall separation of the curves. It's early
2 benefits, median benefits, and late benefits. And
3 it's true that in CDER's presentations, you include
4 both. But I think it's quite prominent in CDER's
5 conclusions and summarization that the focus moves
6 to the medians.
7 DR. JENKINS: Can we have up slide -- first
8 I want to go back to the safety issues because you
9 spent some time this morning on the safety issues.
10 Can we have backup slide 82? This is the
11 boxed warning that's in the Avastin label
12 currently. Do you agree that this is an accurate
13 representation of the serious safety risk for
14 Avastin, including gastrointestinal perforations,
15 surgery, and wound healing complications, and
16 hemorrhage?
17 DR. HORNING: Yes. As with most agents that
18 are approved in breast cancer, Avastin has a black
19 box warning.
20 DR. JENKINS: But you agree that these are
21 serious and potentially life-threatening risks
22 associated with the use of this drug that warrant a

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1 boxed warning specifically for Avastin?
2 DR. HORNING: Yes. We have said that
3 Avastin has serious side effects that are in line
4 with other agents approved for metastatic breast
5 cancer, including a black box warning.
6 DR. JENKINS: And did Genentech agree to
7 this boxed warning language, or did FDA order you
8 to implement this language for the safety risk?
9 DR. HORNING: We agreed.
10 DR. JENKINS: Thank you.
11 Can we have slide 100 from the FDA main
12 presentation yesterday? Slide 100.
13 This is the absolute difference in the
14 magnitude of PFS across the trials that have been
15 submitted. Do you agree that these data accurately
16 represent the median progression-free survival seen
17 in these trials?
18 DR. HORNING: Yes. These are the median
19 numbers that were taken from the Kaplan-Meier
20 curves.
21 DR. JENKINS: Thank you. And also,
22 slide -- from the main presentation yesterday of

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1 Dr. Keegan, slide 125. This is a slide that was
2 prepared by Genentech, an analysis that was
3 presented by Genentech of the combined results of
4 the survival data from all the first-line treatment
5 trials. So this is E2100, AVADO, RIBBON 1.
6 Do you agree that this is the slide
7 Genentech prepared?
8 DR. REIMANN: Yes. This is the slide
9 Genentech prepared. And I think something you need
10 to know is that the data maturity of the studies
11 differed, and that in RIBBON 1 and AVADO, there
12 were very few patients still at risk in the
13 right-hand portion of this curve.
14 DR. JENKINS: So the hazard ratio for
15 overall survival is accurate at 0.97, with a
16 confidence interval from .86 to 1.08 and a p value
17 of .56? That's accurate?
18 DR. REIMANN: That is correct. And we have
19 updated data with also the most AVADO survival
20 experience, which I could share if you like.
21 DR. JENKINS: So you would agree with the
22 statement that there is no demonstrated overall

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1 survival advantage for Avastin in first-line
2 metastatic breast cancer?
3 DR. REIMANN: Yes. As an efficacy endpoint,
4 there is no statistically demonstrable advantage in
5 overall survival. When it comes to benefit-risk
6 and you're trading off toxicities, then I think
7 looking at early survival or 1-year survival is
8 meaningful.
9 MS. CARTWRIGHT: Just a moment, please.
10 [Pause.]
11 MS. CARTWRIGHT: That concludes our
12 questions. Thank you.
13 Questions by Advisory Committee and
14 Presiding Officer
15 DR. MIDTHUN: Thank you very much.
16 Then we will move on to the next portion,
17 which will be an opportunity for the advisory
18 committee members and myself to ask questions of
19 the Genentech panel.
20 So questions? Dr. Wilson?
21 [Pause.]
22 DR. MITHUN: Can you restart the timer,

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1 please?

2 DR. WILSON: So I would like to ask several

3 things. Obviously, as a member of ODAC, our focus

4 is going to be on the safety and effectiveness of

5 these various trials, and the regulatory aspect in

6 terms of what happened when is really not going to

7 be our focus.

8 I think that what I heard from the panel is

9 that you would agree that the magnitude of the

10 effect was an important endpoint, and that

11 therefore is going to be the focus of your

12 confirmatory trial. And so my focus really is

13 going to be on E21 because I think the question

14 isn't whether or not the "confirmatory trials" are

15 clinically meaningful -- because I think I just

16 heard from you that it wasn't, and I think all of

17 us as oncologists would certainly agree that

18 prolonging progression-free survival by less than

19 one month in the AVADO trial does not constitute a

20 clinically meaningful endpoint.

21 So I think the question at hand, really, is

22 around the confidence that the E21 trial may in

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1 fact not be an outlier. And I think none of us

2 want to lose the possibility that there could be a

3 benefit. However, there are some issues that have

4 come up with regard to this clinical trial, and one

5 of them is that it was unblinded. And we heard

6 data about how blinded and unblinded trials, et

7 cetera, don't necessarily result in biased

8 outcomes.

9 So what I would like to understand and have

10 Genentech address is the following. In the E21

11 trial, the median duration of paclitaxel treatment

12 was 5.1 months, and the median time of progression

13 was called at 5.9 months. The median time of

14 treatment for the combined paclitaxel and Avastin

15 was 7.1 months, but progression wasn't called until

16 11.8 months.

17 So I see a very large difference between

18 stopping the control arm and calling progressive

19 disease versus stopping the treatment arm and

20 calling progressive disease. And I'm just curious

21 because this could represent investigator bias in

22 terms of when scans were done, looked at,

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1 et cetera.

2 DR. REIMANN: First let me address the

3 timing of scans issue, and then I'll hand off to

4 Dr. Horning. I think in your preamble you also

5 said that all of us as oncologists would agree that

6 the confirmatory studies don't express benefit, and

7 there I think I would respectfully disagree because

8 the 2.9-month prolongation in PFS in RIBBON 1 and

9 capecitabine we think is meaningful, given the side

10 effect profile and approval in Europe.

11 If we could bring up the slide on the timing

12 of scans in E2100. As mentioned in my core

13 presentation, the timing of scans was balanced

14 between the control arm and the Avastin arm.

15 Yes, that's the slide. Please bring that

16 up.

17 So we see here that at the first year

18 assessment, 2.6 months and 2.7 months to the first

19 scan; second assessment, 5.4/5.5; 8.2/8.2;

20 11.1/11.0; 13.6/13.8. So with that aspect, the

21 scans were balanced.

22 DR. HORNING: Well, I think the only other

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1 point to be made is that it's not clear that it's

2 appropriate to extrapolate from chemotherapy time

3 from completing treatment to time of progression,

4 to a combination of chemotherapy plus a biologic

5 agent that may have a very different mechanism of

6 action as it relates to the pace and the underlying

7 biology of disease progression. But I do believe

8 that Dr. Reimann addressed your question about the

9 potential bias in scans.

10 DR. WILSON: Well, actually, no. I think

11 you simply gave me times that these scans were done

12 at, on average. However, that doesn't get into the

13 nitty-gritty of this. I guess my response to the

14 interaction would be that such an interaction was

15 not seen in the AVADO trial, where I would also

16 have expected to see a longer duration of response

17 in the combination arm relative to when the drug

18 was stopped, and I don't think we necessarily saw

19 that.

20 The second question I wanted to get at was

21 the overall toxicity. We have seen much summary

22 toxicity, and numbers of slides were shown that

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1 indicated that CDER has overstated a number of the
 2 known toxicities and that some of these are seen on
 3 the control arms as well.
 4 Again, because my focus is the E21 trial
 5 because, again, I think that is the trial that most
 6 of us would agree shows clinical benefit. With all
 7 due respect to Genentech, .8 months in most
 8 clinical oncologists' minds is not clinical
 9 benefit.
 10 I'd like to turn to the toxicity that
 11 actually is reported in the E21 trial. And if you
 12 actually look at that, you can see that there is
 13 very clear signal of increased toxicity in the
 14 treatment arm. In fact, if we look at infection in
 15 terms of grade 3 and grade 4, it's 9.3 percent
 16 versus 2.9 percent for the control arm. If we look
 17 at hypertension, it's 14.5 percent versus
 18 zero percent. I would contend that hypertension is
 19 not a benign finding; although it may be
 20 controlled, it requires the patient to come in for
 21 multiple visits, increases anxiety, et cetera.
 22 Cardiovascular ischemia was 1.9 percent in

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1 the treatment arm versus zero percent in the
 2 control arm. Hemorrhage was .5 percent versus zero
 3 percent in the control arm. And gastrointestinal
 4 perforation was .5 percent versus zero percent.
 5 These are the actual data from the actual
 6 New England Journal study of the trial that I think
 7 we all agree is the main trial that putatively
 8 shows that this is an effective drug.
 9 Perhaps you could comment on that in light
 10 of your summary data, which at least it was very
 11 unclear to me how to look at that data because it
 12 seemed like there was a lot of statements that
 13 these sorts of toxicities were seen on both arms
 14 equally. At least, that's the kind of general
 15 sense I got.
 16 DR. HORNING: A number of issues that you've
 17 brought up. You yourself mentioned that the time
 18 on treatment was longer for the patients receiving
 19 paclitaxel plus Avastin versus paclitaxel alone.
 20 And I think that as we're looking across the
 21 toxicities, we need to think about those that might
 22 be related to the underlying chemotherapy, the

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1 combination, or perhaps Avastin alone.
 2 With regard to the summary that was
 3 presented this morning, there's no doubt that
 4 hypertension occurs with Avastin and doesn't occur
 5 with chemotherapy. And we've presented the
 6 available data from an expert panel with regard to
 7 its management. We've presented data from the CO8
 8 study regarding its reversibility. And we
 9 certainly heard from patients yesterday about how
 10 troublesome hypertension is to them in their daily
 11 lives with management, which I think is probably
 12 the best testimonial of all.
 13 We also described that the incidences in the
 14 pooled safety data, which I believe is important
 15 because it reflects the totality of the data. And
 16 when you think about E2100 and when it was
 17 conducted, it was very early on in the use of
 18 Avastin. And just as with any other medications,
 19 physicians become more refined in their clinical
 20 judgment as time goes on.
 21 But nonetheless, there are increases, as we
 22 mentioned, in toxicities such as bleeding,

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1 congestive heart failure, and arterial
 2 thromboembolism that are in the range of a 1.2 to
 3 1.6 percent increase, somewhat more so in the E2100
 4 trial. And the other adverse events are occurring
 5 with a lesser incidence, less than 1 percent, and
 6 they do occur in the pooled analysis on both the
 7 chemotherapy and the chemotherapy plus Avastin
 8 arms.
 9 But I have to say that with regard to
 10 hands-on clinical experience, probably the person
 11 who's best able to describe this for us, for the
 12 ODAC panel, for the entire audience, is someone who
 13 does this on a day in and day out basis, and that's
 14 treat patients with metastatic breast cancer with
 15 paclitaxel plus Avastin.
 16 So I'd like to ask Dr. O'Shaughnessy if she
 17 could comment.
 18 DR. O'SHAUGHNESSY: Thank you. Obviously,
 19 these toxicities are very, very important, no
 20 question about it. Hypertension is definitely
 21 there. We've learned to recognize it early, get
 22 patients on therapies that are very, very well-

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1 tolerated, such as hydrochlorothiazide, lisinopril,
2 very easy for patients. It generally works. It's
3 the rare patient who's already started with some
4 predisposing hypertension that isn't well-
5 controlled. But we get the patient to the
6 cardiologist. We get the help. So it's very, very
7 manageable, honestly.

8 The other more serious things are things
9 that we think about very, very carefully. It
10 really boils down to patient selection. And I must
11 say, being just a breast cancer doctor, I've had
12 less experience with bevacizumab, Avastin, than
13 docs in the general community because they get to
14 use it for lots of indications.

15 But my own learning curve has been very
16 good. There has been a learning curve. But I will
17 tell you, just really, really carefully asking
18 people about prior history of diverticulitis, for
19 example. What's their history of arterial vascular
20 disease? Longstanding hypertension; big-time
21 smokers. You really have to weigh those risks and
22 benefits. Not that you don't sometimes have to

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1 prescribe it nonetheless, depending on the severity
2 of symptoms, for example, but you've got to weigh
3 that risk-benefit. And I think that it's very,
4 very doable, honestly, in practice.

5 DR. WILSON: I just have two more, and then
6 I'll be done.

7 So the hypothesis is that there is a
8 specific interaction between Avastin and a specific
9 taxane. I think we know that from comparative
10 trials between docetaxel and paclitaxel, that there
11 are some scheduled dependencies in terms of
12 effectiveness. But in numbers of these studies,
13 they've actually come out with docetaxel as being a
14 somewhat more effective agent.

15 When I look at the AVADO trial, and I look
16 at the hazard ratios among those patients who have
17 received therapy but have not received prior taxane
18 therapy, and I look at the group that got
19 15 milligrams of bevacizumab, the hazard ratio is
20 really about .7, .8. And it's only in the group
21 that has had prior taxane where the hazard ratios
22 now move more toward favoring the combination. And

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1 a similar trend is seen in the E21 trial as well.

2 So I'm curious what you think about this
3 because my interpretation of this, just purely as a
4 scientific evaluation, is that synergy of two
5 agents, where both agents are active, should really
6 be showing up most when the agents are fully
7 active. And yet when they have not had prior
8 taxanes, that's when it looks like the activity of
9 the combination is least effective; whereas in
10 patients that are perhaps more resistant to the
11 taxanes, as reflected by having prior taxane
12 therapies, that's where the hazard ratios favor the
13 combination.

14 This would suggest to me that what's
15 happening is that what's driving the deltas in the
16 hazard ratio is actually a fall in the control arm
17 and not an improvement in the treatment arm.

18 DR. HORNING: I presented the schema for the
19 E2100 trial, and the investigators at that time
20 projected that the control arm would have a median
21 PFS of six months. The actual PFS was very close
22 to that. In addition, if you look at the

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1 projections across the other studies for the
2 RIBBON 1 studies, they also were very similar to
3 the projections. So there really isn't any data in
4 the outcomes of the studies that suggested that the
5 control arms performed any less well than
6 projected.

7 The other thing to note is that you're
8 correct in saying that prior exposure to taxanes
9 was associated in the forest plots with an improved
10 or more favorable hazard ratio for AVADO and E2100,
11 but that was not true for RIBBON 1 docetaxel.

12 DR. WILSON: And then my final question --

13 DR. HORNING: Dr. Wilson, I also wanted to
14 just get back to another thing that I failed to say
15 earlier that might be informative. When you asked
16 me about the time of exposure of Avastin versus
17 paclitaxel plus Avastin in E2100 and that sort of
18 increment until progression, I think the other
19 thing that I failed to say, which is important, is
20 that unlike chemotherapy, where it's on or its off,
21 that with Avastin we're talking about something
22 that has a 20-day half-life.

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1 DR. WILSON: Right. And so my final
 2 question is, one of the endpoints of your new trial
 3 is to try to determine biomarkers of outcome. And
 4 I do hope, if your hypothesis, which is being drawn
 5 from the AVADO trial, is correct, that you would in
 6 your new trial power it such that you're going to
 7 see this effect in the top 50 percent of VEGF
 8 expressors.

9 But having said that, there was an analysis
 10 done on the E21 trial where they looked at VEGF
 11 genotype and overall survival. And what they found
 12 in that paper, that was published in the Journal of
 13 Clinical Oncology, was that a favorable genotype
 14 that resulted in a better outcome was only seen in
 15 7.6 percent of patients. That was the AA
 16 polymorphisms at the 2, 5, 7, 8, and 1154 loci. By
 17 contrast, harm was noted in 21.5 percent of
 18 patients with CAGG polymorphisms at these loci
 19 because their survival was actually less than the
 20 entire cohort.

21 Obviously, this raises concern that any
 22 hypothesis about VEGF needs to incorporate

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1 polymorphisms, but it also raises the question of
 2 whether or not we are actually -- if the E21 trial
 3 is not correct, that we actually, by continuing to
 4 allow this study, this drug, to stay on accelerated
 5 approval, that we may in fact be harming more
 6 people than we're helping.

7 DR. HORNING: Yes. I'd like to address that
 8 question in the following way. Dr. Wilson is
 9 referring to a paper written by the E2100
 10 investigators looking at single nucleotide
 11 polymorphisms. And they did not have plasma
 12 collections on the patients; rather, they went to
 13 the tumor tissue. And in their analysis, they did
 14 not look at both arms of the study; they only
 15 looked at the patients who were receiving Avastin
 16 plus paclitaxel. And there they made the
 17 associations that Dr. Wilson is referring to.

18 We have had an opportunity to look at these
 19 polymorphisms, first in a trial called AVITA, which
 20 is in pancreas cancer, and we were unable to
 21 confirm the findings in that study. Next we went
 22 to the AVADO study, where we do have plasma. And

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1 we not only looked at these polymorphisms, but we
 2 looked at a large panel of polymorphisms. We're
 3 unable to confirm the findings of E2100, and the
 4 results have been submitted with Dr. Miles as the
 5 first author for the ECCO ESMO conference this
 6 fall.

7 DR. MIDTHUN: Yes, Dr. Balis?
 8 DR. BALIS: Thank you.

9 I gather from the comments that were made
 10 from a couple of speakers that meeting the primary
 11 endpoint in this trial meant finding a
 12 statistically significant difference. And I'd like
 13 to ask whether you think that finding a
 14 statistically significant difference equates to a
 15 clinically significant outcome.

16 DR. REIMANN: I'll hand it over to
 17 Dr. Horning in a moment. But no. The fundamental
 18 question is, was the study positive, and that's
 19 what we look at with the primary study analysis.
 20 We also power a study to make sure that these
 21 studies, especially if it's a single study for
 22 approval, is a substantial study that lets you look

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1 at subgroups and secondary endpoints, et cetera.
 2 But at the end of the day, it is a clinical
 3 judgment about magnitude of effect.

4 DR. BALIS: SO the term was used --
 5 DR. HORNING: I'll just also add that these
 6 studies were designed with breast cancer
 7 investigators, and the feeling at that time was
 8 that a treatment effect with hazard ratios in the
 9 .7 to .75 range would be clinically relevant in
 10 terms of treatment benefit for patients with
 11 metastatic breast cancer.

12 If we could just indulge in finishing this
 13 answer, maybe Dr. O'Shaughnessy could speak to that
 14 issue of clinical benefit, hazard ratio, and
 15 treatment effect in metastatic breast cancer.

16 DR. O'SHAUGHNESSY: Yes. This is a very
 17 important issue. The progression-free survival
 18 benefit, when we see .65, .7, we know that that
 19 treatment has perturbed the natural history of
 20 metastatic breast cancer, and that means it's
 21 important. Inevitably, it's a subset of patients
 22 who benefit. So then how do you translate that

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1 into clinical benefit that we all believe in?
 2 First-line metastatic is very difficult to
 3 show survival advantages, as we heard from
 4 Dr. Reimann, because of the duration that most
 5 patients live after first line. So survival is
 6 difficult.
 7 We would like to have better quality of life
 8 measurement tools for symptom reduction and also
 9 prevention of symptoms because these are the things
 10 that we are tasked with doing for our patients. If
 11 we can't necessarily improve survival, or even if
 12 we can, preventing symptoms, reducing symptoms, our
 13 tools just don't seem to be where they need to be
 14 although, frankly, we need greater emphasis on
 15 that. No question about it.
 16 So from a clinician, we want agents that
 17 definitely perturb the natural history because, as
 18 you well know, we're in this transition period from
 19 breast cancer trials that have been done with
 20 heterogeneous populations, and there's a lot of
 21 work going on at the subpopulations that lead to
 22 additional hypotheses. So we clinicians are

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1 figuring it out, if you will.
 2 But I just don't think our measurement
 3 tools, truthfully, for first-line metastatic breast
 4 cancer with regard to clinical benefit, are as
 5 well-established as we would like..
 6 DR. BARRON: Can I just add one thing, too?
 7 Because I've made some of these comments. And if
 8 we could put the slide back up that you had.
 9 I think it's particularly important to
 10 address your question. There's no question that
 11 you can have a statistically significant effect
 12 that's not clinically meaningful. However, it's
 13 also possible that you have a statistically
 14 significant effect that is clinically meaningful.
 15 And the reason we are focused on hazard ratios here
 16 is that what you heard -- and Dr. Schenkein's quote
 17 supports this.
 18 When E2100 was first unblinded and described
 19 to the world, this hazard ratio of .48 is
 20 unprecedented. It is extremely robust. We then
 21 observed in AVADO a hazard ratio of .62. It is
 22 less, but it's only somewhat less. And the point

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1 that we are trying to make is that .62 is a very
 2 significant hazard reduction. The studies were
 3 planned to have a hazard of .7 to .75 to represent
 4 clinical benefit. This far exceeds that.
 5 So all we're concluding, and what we said,
 6 is we're not trying to convert E2100 to full
 7 approval. We're just stating that we don't think
 8 AVADO and RIBBON 1 invalidate the findings of
 9 E2100. And this hazard ratio of .62 is exactly why
 10 we state we don't think it invalidates the findings
 11 of E2100.
 12 DR. BALIS: So I think at the end there we
 13 talked about getting down to that last question as
 14 to what we do in terms of proceeding forward with
 15 the current accelerated approval while you
 16 potentially study the drug. The way that I took
 17 what was being said from that discussion was that
 18 if we're unsure, then we shouldn't withdraw the
 19 approval. We should conduct a study to make sure
 20 that we are sure.
 21 So my question to you, as having looked at
 22 this data better anybody, are you sure or are you

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1 unsure as to whether this drug provides a clinical
 2 benefit that outweighs the risk of the drug?
 3 DR. HORNING: Well, as provided on my
 4 assessment slide of clinical benefit-risk, we are
 5 saying that Avastin plus paclitaxel in first-line
 6 metastatic breast cancer provides a favorable
 7 clinical benefit-risk. And we say that on the
 8 basis of the E2100 results. It's a well-conducted
 9 study, robust results; that AVADO and RIBBON 1 do
 10 not invalidate these results. And we have a safety
 11 profile with no new findings.
 12 So the E2100 results have not changed, and
 13 the safety profile has not changed. And we feel
 14 that the favorable clinical benefit-risk ratio, the
 15 favorable clinical benefit maintains for paclitaxel
 16 plus Avastin.
 17 MR. LABSON: I would just add from the
 18 regulatory perspective that we're not saying
 19 accelerated approval should be maintained just if
 20 one is unsure, but because the data show that
 21 there's a reasonable likelihood of benefit. And
 22 it's really based on that as the standard that's in

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1 the law.
 2 DR. MIDTHUN: Dr. Sekeres next, and then
 3 Ms. Portis.
 4 DR. SEKERES: Thank you so much. I was
 5 hoping to focus on two areas.
 6 Would it be possible to put up slide 97 from
 7 the company?
 8 I wanted to talk a little bit about overall
 9 survival because I think when we're talking about
 10 the effects of Avastin combinations, there are a
 11 couple of different focuses we've had during this
 12 meeting. One has been on what is the minimal
 13 acceptable effect to get approval from the FDA, and
 14 we've talked about median progression-free survival
 15 and hazard ratio. And then there's the effect
 16 that's going to be a benefit to patients that we
 17 can measure.
 18 At the last ODAC when we met about this
 19 issue, almost a year ago, we talked about
 20 progression-free survival and how, if that were
 21 paired with patient-reported outcomes that were
 22 also positive, that may be a beneficial effect to

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1 patients. In the absence of that, the gold
 2 standard for effect is overall survival, and that a
 3 progression-free survival without patient-reported
 4 outcome or quality of life improvement and without
 5 overall survival may just be a Pyrrhic victory.
 6 So I was hoping to gain some insight into
 7 this slide. Was the point of showing this to say
 8 that it would be impossible to do an overall
 9 survival study in first-line metastatic breast
 10 cancer?
 11 DR. REIMANN: No, that's not the point of
 12 the slide. And I just want to address your whole
 13 question because you talked about patient-reported
 14 outcomes and survival and PFS.
 15 I think, first, we believe that a large
 16 magnitude of PFS benefit is clinical benefit in
 17 this setting. And we've heard that from FDA, that
 18 a large magnitude of PFS benefit is clinical
 19 benefit. We realize that there are some other
 20 perspectives out there, but that's the guidance we
 21 have from FDA.
 22 The point of this slide is to say that in

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1 the front-line setting, most studies performed by
 2 Genentech or performed by any other sponsor that
 3 typically have sample sizes of 500 to 800 patients
 4 are not optimally powered for survival. They do
 5 have a certain amount of power, and I'm not in any
 6 way suggesting we go to lowest common denominator
 7 studies of 2- or 300 patients. That's not the
 8 intent here.
 9 What I'm saying is that there could be a
 10 real survival benefit, and you're not going to be
 11 able to detect it because of the dilution effect
 12 and because of the variability. And I think a
 13 four-month prolongation in median overall survival
 14 would be very important. It's on the order of what
 15 was seen with Herceptin in first-line metastatic
 16 breast cancer, but we see that in order to detect
 17 that magnitude of benefit, we would need studies on
 18 the order of 1500 to 2300 patients.
 19 It's doable. It's just they're very big
 20 studies. And when we consider that PFS of a large
 21 magnitude has benefit on itself, we have to
 22 question where we're expending our patient

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1 resources.
 2 DR. SEKERES: So again, I think we're mixing
 3 a little bit about a regulatory threshold with
 4 what's a direct benefit to women. To say to a
 5 woman, congratulations, you haven't progressed with
 6 your breast cancer, in the absence of having any
 7 quality of life improvement, still remains a
 8 Pyrrhic victory to me. And conducting a study of
 9 2,000 women powered on overall survival when, as
 10 you pointed out, there are 45,000 women diagnosed
 11 with this in the U.S. each year and many-fold more
 12 than that internationally, doesn't seem impossible.
 13 To me it seems like the right thing to do.
 14 I also wanted to move on.
 15 Dr. Horning, you asked us if there's one
 16 slide we should remember, it should be this one.
 17 And I actually remembered it, slide 26 from the
 18 presentation.
 19 So when you talk about fewer total deaths,
 20 could you just clarify for me, are those deaths on
 21 study?
 22 DR. REIMANN: That's deaths at any time. We

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1 do survival sweeps, but not on study. It's any
2 time.
3 DR. SEKERES: So you continue to record
4 deaths after a patient has gone off study and gone
5 on to other therapies?
6 DR. REIMANN: Yes. So the death events come
7 from the overall survival analysis, where you
8 assess all deaths, whether on study -- technically
9 speaking, the patients are still on study because
10 they still have survival follow-up.
11 DR. SEKERES: So on the E2100 study, there
12 are still 25 to 30 percent of women who are still
13 alive?
14 DR. REIMANN: The definitive analysis of
15 overall survival on the E2100 was 481 deaths. And
16 so your percentage is approximately correct.
17 DR. MIDTHUN: Dr. Freedman?
18 DR. FREEDMAN: Thank you.
19 Dr. O'Shaughnessy mentioned the fact that
20 triple negative is highly symptomatic in most
21 patients. I think that's correct. And also that
22 improving or decreasing patient symptoms with the

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1 least amount of toxicity is a major objective. And
2 yet we didn't see any of this in the studies.
3 I just wondered -- my first question is what
4 you feel about that, the results without that
5 representing clinical benefit.
6 DR. O'SHAUGHNESSY: I think one of the
7 important approaches is to look at these patients
8 who we know clinically have a lot of symptoms.
9 Like the triple negative is, arguably, the patients
10 with HER2-negative disease that collectively have
11 the highest burden. It's just the tempo of their
12 disease and the sites of metastases.
13 When you see nice benefits in PFS in those
14 patients and higher response rates, you can be
15 pretty certain that that's translating into
16 clinical benefit in those patients, just because
17 the burden of disease is so great in those
18 patients. So that to me makes it that easy.
19 The aggressive ER-positives, though, we
20 don't want to forget them, very, very virulent
21 disease, with a natural history almost as bad as
22 triple negative disease. Heavily burdened. It's

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1 the indolent ER-positives that live without
2 symptoms for long periods of time.
3 DR. FREEDMAN: Were you disappointed not to
4 see any symptom improvement in this subgroup of
5 patients presented from this trial?
6 DR. HORNING: Let me just preface that by
7 saying that certainly quality of life is extremely
8 important for patients, and it's very important for
9 the physicians who take care of them. And we do
10 not have quality of life data that meet CDER's
11 standards from our first-line metastatic breast
12 cancer trials. Actually, meeting the standards is
13 very difficult because we don't have validated
14 instruments and because there are always issues of
15 missing data based on patient death and
16 progression.
17 If you actually look at the record for being
18 able to determine quality of life to the place
19 where it can be acceptable in the U.S. product
20 labeling, the track record -- if we could show the
21 slide -- for metastatic breast cancer is as it is,
22 which is that in all of these agents that are

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1 approved, quality of life was included in the
2 studies.
3 But with regard to the limitations that we
4 have with the instruments, with missing data, and
5 the fact that in first-line metastatic breast
6 cancer, many patients who actually enter the trials
7 are not currently symptomatic, we're not able to do
8 those. Nonetheless, quality of life is an
9 extremely important measure, and we will be
10 including quality of life measures in our planned
11 confirmatory trial.
12 DR. FREEDMAN: My next question is related
13 to the future trial, the proposed trial. And,
14 obviously, the results of E2100 are the basis for
15 this trial, for the parameters that you use there.
16 You got a response rate of 21 percent for
17 weekly paclitaxel. And again, I ask
18 Dr. O'Shaughnessy, is that what you would expect in
19 a population of patients who had metastatic breast
20 cancer who had limited, fairly limited, prior
21 exposure to Taxol as an adjuvant, of course, only?
22 Just wondering what -- and also if you consider

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1 that the control arms of the subsequent studies had
 2 much higher responses. And I'm just wondering how
 3 relevant or significant the difference between the
 4 control arm and the study arm actually is.
 5 DR. O'SHAUGHNESSY: I believe the data on
 6 E2100. I'm not surprised by the 21 percent on the
 7 weekly paclitaxel. These trials, as you know, have
 8 various patient populations. E2100 had 32 percent
 9 triple negative patients. Two-thirds had had
 10 adjuvant chemotherapy. I'm not surprised. Of
 11 course, there'll be variability around that point
 12 estimate, of course. But no, I'm not surprised by
 13 that.
 14 DR. FREEDMAN: But generally speaking, you
 15 would expect a higher response rate with weekly
 16 paclitaxel.
 17 DR. O'SHAUGHNESSY: Not necessarily.
 18 DR. FREEDMAN: All right. Let's consider,
 19 then, that we had information about the treatment-
 20 free interval on these patients. And I asked the
 21 question yesterday, actually, and probably could
 22 bring it up again today, is do you have data, does

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1 Genentech have data, on the difference in response
 2 rate in those patients who were less than 12 months
 3 with a treatment-free interval, in other words,
 4 indicating some degree of resistance to Taxol,
 5 potentially?
 6 DR. O'SHAUGHNESSY: No.
 7 DR. FREEDMAN: Thank you.
 8 DR. MIDTHUN: I think, Ms. Portis, you had a
 9 question?
 10 DR. PORTIS: Just following up on a couple
 11 things. I very much appreciate the testimony we
 12 received yesterday from patients, but I want to
 13 remind us all that we are not hearing from patients
 14 who discontinued treatment due to adverse effects,
 15 and we're not hearing from people who died due to
 16 Avastin. And I think the risks are still
 17 significant. And I know now we're talking a lot
 18 about E2100.
 19 So my first question is, would you say that
 20 you then consider that E2100 was a success despite
 21 the fact that there is missing data, there's
 22 discrepancy of interpretations of the scans, there

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1 is no quality of life data, and there is no
 2 improvement in overall survival? I hear people
 3 keep talking about no impairment of overall
 4 survival, but what matters to patients is
 5 improvement in overall survival. So that's my
 6 first question.
 7 DR. HORNING: Let me begin, and then I'll
 8 ask perhaps Dr. Reimann to join in. I think that
 9 with regard to the comments about the toxicities of
 10 treatment for first-line metastatic breast cancer,
 11 they're well-taken. And as mentioned in my
 12 presentation, if we look across all of the
 13 metastatic breast cancer studies, the treatment-
 14 related mortality for standard dose Avastin plus
 15 chemotherapy versus chemotherapy is identical,
 16 1.8 percent and 1.8 percent.
 17 So, unfortunately, there are patients who
 18 have treatment-related deaths due to chemotherapy
 19 or chemotherapy plus Avastin. In this series, it
 20 was equal.
 21 We also recognize that there are differences
 22 of opinion with regard to whether or not

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1 progression-free survival of a sufficient magnitude
 2 provides direct clinical benefit. It's our view,
 3 and it was CDER's view as expressed yesterday and
 4 is CDER's view, I believe, that in first-line
 5 metastatic breast cancer, progression-free survival
 6 of sufficient magnitude without a statistically
 7 significant improvement in overall survival or
 8 quality of life data provides direct clinical
 9 benefit.
 10 With regard to E2100 and some of the issues
 11 that Dr. Reimann addressed in his presentation
 12 today, I'll ask him to complete your question.
 13 DR. REIMANN: I think your question was more
 14 about the magnitude of efficacy in E2100. And,
 15 yes, we do feel that the study was a big success,
 16 just like many other cooperative groups, that has
 17 led to labeling for the medication.
 18 I think the aspects of it I think are
 19 important, the large benefit in progression-free
 20 survival, doubling an objective response rate. And
 21 really, every way we've looked at the data through
 22 sensitivity analyses, we see a similar magnitude

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1 effect. And so we know this is a solid study, and
2 we believe the study will be confirmed.
3 As far as overall survival, as I discussed
4 in my presentation, I think it's specifically
5 challenging in the first-line setting. That
6 doesn't mean we shouldn't try it, but I think the
7 long post-progression survival makes it difficult
8 for this or any agent to demonstrate benefits. I
9 think all of us like four months; we think it would
10 be important.
11 Really, I think it's the impact of multiple
12 medicines over multiple lines of therapy that will
13 move survival forward. And we've seen that in the
14 epidemiological data. You can't attribute that to
15 any specific drug. It is epidemiological data.
16 But I do really feel that over the last 20,
17 30 years, we have made progress.
18 DR. BARRON: Can I just add one more point
19 that I think is important? It's absolutely true
20 that there was no statistically significant
21 improvement in overall survival in E2100, as you
22 point out. But it is important to note that the

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1 hazard ratio was, I think -- maybe we could pull it
2 up -- .87, with a p value of .14.
3 You've heard the challenges in powering
4 trials to show statistical significance. And I
5 think it was one of the people who made a
6 testimonial yesterday who said something that I
7 think we need to remember, which is, the absence of
8 evidence is not evidence of absence. These
9 observations, had they been powered, may -- or may
10 not; we can't know for sure -- demonstrate a
11 survival advantage.
12 What we see at one year is a 7.4 percent
13 absolute benefit in terms of overall survival, with
14 confidence intervals that exclude zero. We can't
15 ignore that data point. Maybe we can bring up the
16 slide. You've seen it.
17 I don't mean to disagree with the
18 statistical fact because it's absolutely correct
19 that we have not seen a statistically significant
20 improvement in overall survival. But I do think
21 that the data is most consistent with benefit
22 rather than no benefit. And we just need to take

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1 into account and understand fully the comments that
2 Dr. Reimann made about the challenges in
3 interpreting underpowered assessments.
4 DR. PORTIS: The 1.8 that you mentioned,
5 that's over what period of time?
6 Dr. Horning, you used that number, 1.8, of
7 survival.
8 DR. HORNING: So we just talked about the
9 safety assessments and when they were made. It's
10 the same time period.
11 DR. PORTIS: Just a couple other things. So
12 you continue to maintain that the risks are low,
13 both adverse events and death and early death due
14 to treatment with Avastin. And so my question is,
15 are you saying that you're comfortable with a risk
16 for patients in continuing to administer Avastin,
17 especially if potentially this study that you're
18 talking about wouldn't be completed until at least
19 2016? And are you comfortable with women
20 continuing to bear those risks and the deaths that
21 may come about with that much more time studying
22 this drug? Because I think part of what I thought

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1 we did in July, those last studies -- it sounds
2 like we're not talking about that much right
3 now -- were supposed to give us more data.
4 DR. HORNING: Absolutely. We're very
5 comfortable with this because, once again, the
6 deaths are not any different in the experience with
7 our first-line metastatic breast cancer in terms of
8 treatment-related mortality. And there are fewer
9 deaths overall with E2100. So yes, we're
10 comfortable.
11 The numbers are 52 percent deaths -- excuse
12 me -- 70.5 percent deaths on E2100 versus
13 73.9 percent with paclitaxel alone. Yes, could you
14 put the slide up? And clearly, Avastin does have
15 serious side effects. We acknowledge that, and we
16 think that those side effects are in line with
17 other treatments for first-line metastatic breast
18 cancer.
19 We also feel that the product guidelines
20 serve to guide physicians in the management, and
21 the fact that oncologists who are treating patients
22 with breast cancer have a lot of experience with

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1 Avastin because they're also treating patients with
 2 colorectal cancer and lung cancer. More than a
 3 million patients have been treated worldwide.
 4 Perhaps I could ask Dr. O'Shaughnessy to
 5 also address your question again because she has
 6 such great experience in treating metastatic breast
 7 cancer.
 8 DR. O'SHAUGHNESSY: Yes. I would really
 9 have to say to you that I'm very, very comfortable
 10 with the safety. We've heard very, I think,
 11 exhaustive data here about the death rates and the
 12 safety, and I am personally very, very comfortable
 13 with it.
 14 I think that this would be a great benefit
 15 to women, particularly those, as I pointed out in
 16 my presentation, who have more limited treatment
 17 options for their breast cancer, triple negative
 18 breast cancer, aggressive, people who need
 19 combinations. We would be doing a very great
 20 disservice to women to take this away from them
 21 while this confirmatory trial is being conducted.
 22 DR. MIDTHUN: Dr. Logan?

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1 DR. LOGAN: So I wanted to pursue the issue
 2 of the reliability of the magnitude of the PFS
 3 benefit that is claimed for the E2100 study. You
 4 previously showed that there are comparable
 5 analyses with the investigator progression versus
 6 the independent review assessment of progression.
 7 My question is, how is the missing data
 8 handled in that analysis, particularly when
 9 patients had been identified as reaching
 10 investigator progression, which was unconfirmed by
 11 the Independent Review Committee, and then their
 12 subsequent missing scans? Were they censored at
 13 that point?
 14 DR. REIMANN: Yes. So let me address it.
 15 Let me explain first the endpoint. There were
 16 cases, as with any independent review, where the
 17 investigator progression is not confirmed by the
 18 IRF. That's the reality of doing studies with an
 19 independent review, because patients are generally
 20 managed by the investigator's assessments, so once
 21 there's progression by investigator, you don't get
 22 additional scans.

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1 Actually, this is an aspect we're building
 2 into the confirmatory study, so we will be
 3 continuing to collect tremor assessments even after
 4 the investigator progression until their second
 5 progression.
 6 In E2100, we performed a sensitivity
 7 analysis where, if the investigator progression was
 8 not confirmed, we used the last available scan data
 9 plus one day as the progression day. And the
 10 hazard ratio for that is .46, and the absolute
 11 benefit went from 5 months to 9.2 months, which is
 12 a 4.2-month difference.
 13 DR. LOGAN: I'm a little concerned
 14 about -- there may be some modest differences in
 15 the investigator progression not being confirmed by
 16 the independent committee between the control group
 17 and the Avastin group, from 15 percent versus
 18 9 percent. That's modest, but there may be some
 19 sensitivity analysis that should be considered
 20 there.
 21 So have you done additional sensitivity
 22 analysis? The FDA indicated that the range of

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1 possible effects, in terms of the hazard ratios for
 2 progression-free survival that the sponsor had done
 3 ranged between .48 and .78. I wonder if you could
 4 confirm that.
 5 DR. REIMANN: Yes. As FDA said yesterday,
 6 there are a variety of sensitivity analyses and
 7 they differ considerably.
 8 If I could have the slide that was just
 9 there a moment ago.
 10 I think you have to distinguish between
 11 sensitivity analyses that treat both treatment arms
 12 fairly and sensitivity analyses that treat one
 13 treatment arm different from the other.
 14 If we could have the first table of results,
 15 where we treat the two treatment arms equally. It
 16 was just there a moment ago.
 17 In that analysis of using a number of
 18 different analyses that treated the two treatment
 19 arms equally, we see no difference in the hazard
 20 ratios, and we don't see any difference in the
 21 medians. In analysis where we --
 22 Yes, this is the slide, please. No. Let's

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1 use this one.

2 So first we'll start with analysis that

3 treat the two arms equally. So that would be the

4 first two slides on the -- the two lines on the

5 slides. We see clinical progressions. This means

6 we are basing the decision based on radiographic

7 progression, and the next one is no censoring for

8 non-protocol therapy.

9 In these two analyses -- and we have a

10 number of others that treat the two treatment arms

11 equally -- there is no difference in hazard ratios.

12 You see they're all very similar, around high .47

13 or low, .5. And the difference in absolute benefit

14 is not shown on this slide, but it's about

15 5 months.

16 The other question you asked was, was there

17 some sort of worst case analysis for progressions

18 not confirmed by IRF? That's the bottom row of

19 this table. In this case, we now don't treat the

20 treatment arms equally. And in the control arm,

21 the paclitaxel arm, you see the results are the

22 same, and then the results come in for the Avastin

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1 arm. In this case, you have a hazard ratio of .6,

2 a confidence interval from .49 to .74, and it was

3 very highly statistically significant.

4 If we go to an even more extreme analysis,

5 which is patients not confirmed by the IRF or came

6 off of study for any reason, then the hazard ratio

7 is .78. Now, we do appreciate that that's a very

8 extreme analysis and that point estimate doesn't

9 really reflect truth, but it does show that even in

10 that extreme analysis, there's still a treatment

11 effect.

12 DR. LOGAN: So I understand, of course, the

13 issue with the missing data is you don't know

14 whether you should be treating them in with the

15 extreme case or whether you should be treating them

16 equally. And that certainly casts some questions,

17 I think, about the reliability of the magnitude of

18 the benefit.

19 DR. REIMANN: I think what's striking to me

20 is when we look at all these issues that were

21 raised, the frequency with which those issues are

22 occurring in the control arm and the Avastin arm

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1 were equal in almost every case. So from that

2 perspective, there was no evidence of bias.

3 DR. MIDTHUN: I'd like to ask a few

4 questions. We've had a lot of discussion about

5 progression-free survival. I'd like to ask you,

6 what do you think the magnitude of effect for

7 progression-free survival should be to translate

8 into a clinical benefit for Avastin?

9 I think, also in that, just consider the

10 comment you made earlier, for example, that you

11 accept that the EMEA was through the indication for

12 using Avastin together with docetaxel.

13 DR. HORNING: I think that looking at, if

14 you will, the hazard ratios and median PFS, that

15 hazard ratios that are below a level of .7 and

16 progression-free survivals that are in the range of

17 the Ribbon 1 capecitabine results, which was 2.9 or

18 about 3 months and above, have traditionally fit

19 the bill, if you will, for approvals in first-line

20 metastatic breast cancer.

21 With regard to our plan for the confirmatory

22 study, as you heard from Dr. Reimann, listening to

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1 what we heard from CDER and from the ODAC, we, in

2 fact, are raising the bar.

3 DR. MIDTHUN: Thank you.

4 One other question I have, I believe that

5 you had mentioned in some of the materials you

6 submitted that if the accelerated approval were

7 continued, that you would certainly contemplate

8 label changes, and perhaps a REMs or some other

9 items. And I just wondered if that was, indeed,

10 the case.

11 DR. BARRON: Yes, it is.

12 DR. MIDTHUN: I'd like you to submit that to

13 the docket, if you would, please, what your

14 proposal would be, by July 28th.

15 One other question I had was I noticed that

16 you indicated that there was approval in many, many

17 countries for Avastin. And it seemed that there

18 was a little bit of blackness over there on the

19 right-hand side. And I just wondered, is it also

20 approved in Japan?

21 DR. HELTERBRAND: It is under review right

22 now in Japan.

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1 DR. MIDTHUN: Okay. Thank you.
2 One other question I had was this. What
3 I've heard is that there was agreement at the time
4 of the accelerated approval that AVADO and Ribbon 1
5 could serve as the confirmatory studies. But I
6 wondered, at the time those were actually
7 initiated, which pre-dated the accelerated approval
8 by quite some time, in what context they were
9 submitted to the agency.
10 DR. HORNING: The regulatory history, I
11 believe, is that the E2100 results had been
12 submitted. And there was a request from CDER as to
13 whether any other data would be available. And at
14 that time, the AVADO study was actually complete.
15 And we, as you've heard, shared the top-line data
16 from AVADO at that point in time, at the time that
17 the accelerated approval was granted.
18 With regard to the Ribbon 1 trial, that was
19 submitted to CDER in 2005. There was advice from
20 CDER about independently powering the capecitabine
21 cohort. And then, as you've also heard, the
22 acceptance of Ribbon 1, together with AVADO, as

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1 potentially confirmatory studies.
2 DR. MIDTHUN: One other question, I think
3 you also had in your submission to the docket, and
4 I just wanted to make sure I understood this
5 correctly, that if the accelerated approval were
6 not withdrawn, while you conducted this additional
7 trial, that you would continue the cessation of
8 affirmative marketing for this indication. And I
9 wanted to ensure that my understanding was correct
10 in that regard.
11 DR. REIMANN: We'd certainly be willing to
12 talk to CDER about that, as if we could come to
13 some sort of a middle ground solution that worked
14 to keep the drug as an option for patients.
15 DR. MIDTHUN: Any questions, Dr. Wilson?
16 DR. WILSON: I just very briefly wanted to
17 go back to the overall survival because we've heard
18 several times about an increased percent of
19 patients being alive at one year.
20 On the CDER slide -- could we have slide 58
21 up? I just wanted to show this. Actually, I want
22 number 58 -- 60. I'm sorry, number 60.

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1 So this is the prespecified overall subgroup
2 analysis. And I think that one has to be very
3 careful about at what points one indicates an
4 improvement in survival, because here you can
5 actually see that the treatment arm is actually
6 performing inferior.
7 Then the final slide would be slide
8 number 125. And, again, we've seen this multiple
9 times. But, again, you can see that, depending on
10 where you look at this, it can favor the placebo or
11 the treatment arm. So I just think one has to be
12 very cautious about giving data at one year,
13 because it doesn't give the full picture. It is
14 possible that this actually may worsen outcome in
15 some folks. Thank you.
16 DR. REIMANN: I think there was a question
17 there, so I just want to make sure I address your
18 question, because there were a number of things
19 that flashed up.
20 There was the survival results for the
21 Ribbon 1 taxane cohort, or maybe it was the
22 docetaxel subcohort. And I think we have to be

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1 very cautious at looking at very small subgroups,
2 especially here. There was a 2 to 1 randomization
3 in quite a small control arm. And I think in
4 CDER's own internal review document, their
5 conclusion was that this was an unreliable finding
6 and that you shouldn't have too much emphasis on
7 that. That was actually within their review
8 document.
9 As far as the pooled overall survival as
10 curves, as I showed earlier, the maturity for the
11 AVADO and Ribbon 1 studies on the right-hand side
12 of the curve isn't there. For example, that three
13 years; there's 4 patients at risk in those studies.
14 I do believe that the results in E2100 are
15 meaningful in the early period. And in 3 out of 4
16 studies, we saw a favorable overall survival at one
17 year.
18 DR. MIDTHUN: Dr. Sekeres?
19 DR. SEKERES: Sure. Thank you. I just
20 wanted to comment on something that Dr. Barron
21 said. You were referring yesterday to one of the
22 many brave women who got up and talked about her

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1 experience, and referred us back to the lack of
2 evidence is not evidence of lack, and then referred
3 to the survival curve from the E2100 study.
4 Could we see that survival curve?
5 So in the survival curve, your point was,
6 even though it wasn't a statistically significant
7 difference, there's a chance that the arm
8 containing Avastin could provide a survival
9 advantage, and thus the reference to the quote from
10 yesterday.
11 Could we now see, from CDER's presentation
12 yesterday, slide 41?
13 So in this curve, again, a non-statistically
14 significant difference, but this time the patients
15 who were on the placebo arm seemed to have a better
16 survival advantage. You could just as easily make
17 the argument here that treatment with Avastin
18 actually shortens survival.
19 So I think it's important that we make the
20 point that lack of evidence is lack of evidence.
21 There's no survival advantage with Avastin.
22 DR. REIMANN: Just to respond to your

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1 question in two ways, I think, from the purpose of
2 an efficacy endpoint, we're not making the claim of
3 improved overall survival. It's really in the
4 context of overall clinical benefit-risk that we
5 think this should be discussed.
6 But since the AVADO data has come up a
7 number of times, I did want to share the most
8 recent survival data from the AVADO study,
9 beginning with the standard dose arm.
10 Yes. Data; hazard ratio from the standard
11 dose arm in AVADO has a hazard ratio of .97.
12 Yes. If you could, show this please.
13 DR. CARTWRIGHT: Excuse me. We just wanted
14 to note that the light is red, and also that CDER
15 has not been made aware of this data.
16 DR. MIDTHUN: I think we will have to call
17 this to a close. Thank you very much. And we will
18 now break for 15 minutes, and that will give an
19 opportunity for us to regroup before the next
20 session. So in 15 minutes, which will be 12:30,
21 we'll resume.
22 (Whereupon, a recess was taken.)

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1 DR. MIDTHUN: We will now convene to the
2 last portion before lunch. I think, first,
3 Ms. Cartwright would like to make a clarification,
4 and then we will go onto the 15-minute
5 clarification session. Ms. Cartwright?
6 MS. CARTWRIGHT: Thank you. I just wanted
7 to note for the record that CDER believes that the
8 information Dr. Reimann was about to present was
9 submitted to CDER in 2010. Thank you.
10 Clarifying Questions of
11 Genentech Witnesses by Genentech
12 DR. MIDTHUN: Thank you. So now, we will go
13 onto the clarifying questions, and there will be 15
14 minutes for that opportunity.
15 MR. SCHMIDT: We appreciate that
16 clarification as well. Just a few clarifying
17 questions.
18 Dr. Reimann, I'd like to ask you the first
19 question. You were asked by Dr. Logan about
20 sensitivity analyses for E2100. And I'd like to
21 ask you what you think are the most appropriate
22 sensitivity analyses to use to characterize the

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1 robustness of the magnitude of effect in E2100.
2 DR. REIMANN: Thank you. If we could bring
3 this slide up. I think there are two questions
4 that we look at when we're looking at sensitivity
5 analysis. One is around the magnitude of effect,
6 and one is around whether there is an effect. And
7 I think when looking at magnitude of effect, it's
8 best to look at analyses that treat the two
9 treatment arms fairly. And that's what I'm showing
10 in this slide here. And I'll walk through each of
11 the rows of the table.
12 In each of these analyses, the first two
13 rows of the analyses you mentioned in your
14 question, we have the primary PFS analysis by the
15 independent reviewer hazard ratio of .48; then we
16 have the investigator PFS hazard ratio of .42 and
17 absolute benefit in medians of 5.6 months.
18 The next one is an analysis where we do not
19 censor for non-protocol therapy. So this non-
20 censoring for non-protocol therapy was part of the
21 study analysis plan and agreed with the FDA. It's
22 also a standard practice in the United States and

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1 has been included for the product labeling for
 2 Tykerb and Ixempra. So this is a standard
 3 sensitivity analysis. We do not censor for non-
 4 protocol therapy.
 5 What we see here is a hazard ratio of .57
 6 and an absolute difference in medians of
 7 5.1 months. The next row I think really comes to
 8 your question, which was investigator progressions
 9 that were not confirmed by the independent review.
 10 Here, you see the hazard ratio is .46, very
 11 similar to the primary result, and you see the
 12 medians in both treatment arms come shorter,
 13 because now we're imputing events one day after the
 14 very last tumor assessment in both arms. So that's
 15 kind of a very conservative thing to do, but it's
 16 doing that in both treatment arms.
 17 The reason you see that the number, .46, is
 18 slightly stronger than the .48 of the primary
 19 result is that there was slightly more censoring of
 20 that reason in the control arm, which you noted in
 21 your question.
 22 So what that would tend to do is censoring

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1 on the control arm would tend to bring up the PFS
 2 curve in the tail, which I think you see a little
 3 bit after eight months in the couple of markers;
 4 you see progression-free survival coming up on the
 5 control arm.
 6 The last row of the table is progression-
 7 free survival using the radiographic data only, so
 8 that's not using the clinical exam. There we see
 9 because you're only using some of the data, the
 10 medians move out in both arms.
 11 But in all of these analyses that treat the
 12 two equal treatment arms fairly, we see a very
 13 similar hazard ratio to the primary result and a
 14 very similar absolute benefit. Then the other
 15 analysis that I showed you earlier really gets to
 16 the question about was there an effect under
 17 extreme assumptions.
 18 If we could bring up the next slide?
 19 So it's very important to explain what this
 20 analysis is doing and what it's not doing, because
 21 it's treating the two treatment arms very
 22 differently. You see in the control arm,

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1 paclitaxel, the median PFS is 5.8 months in both
 2 analyses. So if a patient comes off study for non-
 3 protocol therapy or any other reason, they remain
 4 censored in this analysis, in the control arm.
 5 In the Avastin arm, the moment they come off
 6 study for any reason, one day after they've come
 7 off study, they're immediately assumed to have an
 8 event. So this is very extreme, and, of course,
 9 it's unrealistic, because we saw in my main
 10 presentation, a lot of these issues were balanced
 11 almost identically by treatment arm.
 12 But I think what this functions is, as an
 13 extreme analysis of whether there is a treatment
 14 effect. And even under this extreme analysis, we
 15 see a statistically significant effect.
 16 MR. SCHMIDT: Dr. Horning, many of the
 17 questions focused on E2100 and the benefits in
 18 E2100. Why is it that you are confident that E21
 19 represents real and meaningful clinical benefit?
 20 DR. HORNING: We're confident that E2100
 21 provides direct clinical benefit. This clinical
 22 benefit is in line with what we heard from CDER

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1 yesterday, that PFS of a substantial magnitude
 2 defines direct clinical benefit for patients, even
 3 without a statistically significant improvement in
 4 overall survival or quality of life.
 5 E2100 was a well-designed, well-conducted
 6 U.S. study. It was sponsored by the National
 7 Cancer Institute in this country and conducted by a
 8 leading cooperative group. On the safety side, we
 9 have fewer total deaths, fewer MBC deaths, and the
 10 same number of non-breast cancer deaths with E2100.
 11 The common risks, hypertension and
 12 proteinuria, are manageable. There are product
 13 guidelines in our label that allow physicians to
 14 use this safely. Avastin has been widely used, and
 15 the serious adverse events are in low incidence.
 16 We feel on the safety side that Avastin is in line
 17 with other agents used in this indication, first-
 18 line MBC, and most of those agents also have black-
 19 box warnings.
 20 On the efficacy side, we have a treatment
 21 effect in progression-free survival, a hazard ratio
 22 of 0.48, that represents more than a 50 percent

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1 reduction in the risk of disease progression or
2 death. When we look at median PFS, as you've heard
3 many times over the last two days, that's a
4 difference of 5.5 months. We also see a doubling
5 of the response rate. And you heard from Dr.
6 O'Shaughnessy how important that can be,
7 particularly in patients who are symptomatic and
8 heavily tumor-burdened.

9 With regard to the overall survival, if you
10 look at the overall survival curves, you see that
11 they do favor the Avastin plus paclitaxel arm for
12 the first 30 months, after which time they're
13 overlapping. And we've described a 7.4 percent
14 increase in overall survival at one year.

15 When we put all this together, we think that
16 Avastin plus paclitaxel provides a clinical benefit
17 for women with first-line, HER2-negative metastatic
18 breast cancer. We feel these data are supported by
19 the results of AVADO and Ribbon 1, and we note that
20 the EMA and the NCCN agree with this
21 interpretation.

22 MR. SCHMIDT: Final question to Dr. Barron.

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1 Dr. Barron, many of the questions reflect
2 questions over what to do with this dataset and
3 what is the right public health approach faced with
4 this dataset, in terms of withdrawal or continued
5 accelerated approval.

6 Why is it that you believe that the middle
7 ground approach proposed by Genentech is the right
8 public health outcome here?

9 DR. BARRON: Well, as you've heard, we
10 believe that E2100 was a well-conducted study that
11 demonstrated a meaningful clinical benefit. The
12 AVADO and Ribbon 1 studies met their primary
13 endpoint with hazard ratios less than .7 and do not
14 invalidate these findings from E2100. Avastin's
15 safety profile, as you've heard, is acceptable for
16 the indication for which it's approved.

17 Importantly, and we mustn't forget, women
18 with metastatic breast cancer have a devastating
19 and incurable disease with limited treatment
20 options. Maintaining accelerated approval is
21 allowed by law, supported by the science, and
22 clearly in the best interests of patients.

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1 MR. SCHMIDT: Dr. Midthun, those are all the
2 questions we have. We appreciate, on behalf of
3 Genentech, the opportunity to be able to make our
4 presentation today on the science and the law.

5 DR. MIDTHUN: Thank you. We will break now
6 for one hour for lunch, and we will return at 1:40.
7 Thank you.

8 (Whereupon, at 12:42 p.m., a lunch recess
9 was taken.)

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1 AFTERNOON SESSION
2 (1:50 p.m.)
3 Advice and Recommendations from
4 Advisory Committee Members

5 DR. MIDTHUN: Thank you. I am sorry for the
6 delay. We were trying to make the seating
7 arrangements a little bit more workable, so thank
8 you for your patience. We are now beginning the
9 near-final session of this hearing. And this is an
10 opportunity for members of the advisory committee
11 to discuss the issues presented and provide their
12 recommendations.

13 Only the advisory committee members and I
14 will participate in this discussion. If advisory
15 committee members have questions of Genentech or
16 CDER, please direct your questions to me, and I
17 will then direct them to the parties.

18 I will start with the presentation of each
19 of the four questions at issue, and then we will
20 discuss each issue in turn.

21 After the discussion of Issue 1, I will ask
22 the advisory committee members to vote on that

<p style="text-align: right;">Page 205</p> <p>1 issue. And after that, I will ask them to state 2 how they voted and why. We will then repeat that 3 process for the remaining issues. All of the 4 members of the committee, except for the member 5 whose role is to represent the views of industry, 6 may vote.</p> <p>7 As I noted in my opening statement, the vote 8 of the advisory committee represents the 9 committee's recommendation of the agency and will 10 not, of course, decide the issues. Instead, 11 Commissioner Hamburg will consider the advisory 12 committee recommendations, along with the rest of 13 the record, as she makes the final decision.</p> <p>14 So if we could now please put the issues up, 15 I will go through them.</p> <p>16 First, as a reminder, in each question, the 17 indication that is at issue is the one that has 18 been the subject of this hearing; the use of 19 Avastin, in combination with paclitaxel for the 20 treatment of patients who have not received 21 chemotherapy for metastatic HER2-negative breast 22 cancer.</p>	<p style="text-align: right;">Page 207</p> <p>1 for which it was approved and that Avastin has not 2 been shown to present a clinical benefit that 3 justified the risks associated with use of the 4 product for this indication?</p> <p>5 A yes vote means you find that the available 6 evidence demonstrates that Avastin has not been 7 shown to provide a clinical benefit that justifies 8 the risks associated with its use for the breast 9 cancer indication at issue in this hearing. CDER 10 asks for a yes vote. Genentech asks for a no vote.</p> <p>11 Question 3. If the Commissioner agrees with 12 the grounds for withdrawal, set out in Issue 1, 13 Issue 2(a), or Issue 2(b), should FDA nevertheless 14 continue the approval of the breast cancer 15 indication while the sponsor designs and conducts 16 additional studies intended to verify the drug's 17 clinical benefit?</p> <p>18 The Commissioner will reach this issue if 19 she concludes that the grounds for withdrawal or 20 approval set out in one or more of the previous 21 issues has been met.</p> <p>22 On this question, a yes vote means you find</p>
<p style="text-align: right;">Page 206</p> <p>1 Question 1. Do the AVADO and Ribbon 1 2 trials fail to verify the clinical benefit of 3 Avastin for the breast cancer indication for which 4 it was approved?</p> <p>5 A yes vote means you find that the AVADO and 6 Ribbon 1 trials failed to verify the clinical 7 benefit of Avastin for the breast cancer indication 8 at issue in this hearing. CDER asks for a yes 9 vote. Genentech asks for a no vote.</p> <p>10 Question 2(a). Does the available evidence 11 on Avastin demonstrate that the drug has not been 12 shown to be effective for the breast cancer 13 indication for which it was approved?</p> <p>14 A yes vote means you find that the available 15 evidence demonstrates that Avastin has not been 16 shown to be effective for the treatment of the 17 breast cancer indication at issue in this hearing. 18 CDER asks for a yes vote. Genentech asks for a no 19 vote.</p> <p>20 Question 2(b). Does the available evidence 21 on Avastin demonstrate that the drug has not been 22 shown to be safe for the breast cancer indication</p>	<p style="text-align: right;">Page 208</p> <p>1 that available evidence nevertheless justifies the 2 continued approval of Avastin for the indication at 3 issue in this hearing during the time that will be 4 necessary to design and conduct additional studies 5 to verify the drug's clinical benefit.</p> <p>6 A no vote means you think that the available 7 evidence does not justify that continued approval, 8 so that any further investigation of this drug for 9 this use would be conducted under an 10 investigational new drug application. Genentech 11 asks for a yes vote. CDER asks for a no vote. I 12 apologize for the typo there.</p> <p>13 So now, those are the issues. And so what I 14 would now like to do is go back to Question 1, and 15 we will now discuss this issue. And after we've 16 discussed and questions that you have, have been 17 answered, we will then move to vote. But right 18 now, it's open for discussion.</p> <p>19 Dr. Curt?</p> <p>20 DR. CURT: Thank you, Dr. Midthun.</p> <p>21 Accelerated approval is not the ultimate 22 goal for any sponsor; it's full or regular</p>

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1 approval. And we've heard this morning that at the
 2 time of the initial accelerated approval for this
 3 indication, the agency had both the E2100 data and
 4 top-line confidential information about the AVADO
 5 results.

6 I think it's important to remember that in
 7 this period of time, ODAC voted marginally, but
 8 voted nonetheless to deny accelerated approval,
 9 and, yet, accelerated approval was granted. Given
 10 these facts, I can actually understand the
 11 sponsor's impression that FDA implicitly agreed
 12 that the AVADO data was confirmatory. In addition,
 13 I really do believe that if the sponsor had known
 14 that it was important to replicate the E2100 data
 15 as a condition for full approval, they would have
 16 done so.

17 So, Dr. Midthun, I wonder if you could ask
 18 the agency to set these observations in context and
 19 to comment on whether the thinking here has
 20 actually evolved.

21 DR. MIDTHUN: CDER panel?
 22 DR. PAZDUR: What we could say is the

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1 following. At the time that we had met with the
 2 company, we did have the top-line results. As I
 3 stated, we asked the company for these top-line
 4 results in the sense that we wanted to make sure
 5 that the trial had met its primary endpoint.

6 At that time, we had very preliminary
 7 evidence. We had the 24 slides. We were under the
 8 impression that a full dataset was going to be
 9 coming and that we would make a decision on the
 10 clinical benefit, obviously, at the time of receipt
 11 of the entire database.

12 DR. MIDTHUN: Does that answer your
 13 question?
 14 DR. CURT: Yes. Thank you.
 15 DR. MIDTHUN: Yes. Dr. Wilson?
 16 DR. WILSON: I think that what ODAC was
 17 asked to look at, at our last meeting, was the
 18 totality of the data, because at the end of the
 19 day, I believe what we're here to adjudicate is
 20 whether or not we feel that the original study has
 21 been confirmed.

22 My reading of the AVADO and Ribbon studies,

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1 as they were presented to us at the last ODAC
 2 meeting and again today, is that the magnitude of
 3 the effect is smaller than that which was the basis
 4 for approval of E2100, such as with the AVADO
 5 trial, the delta, and progression-free survival
 6 being less than one month; and for the Ribbon 1
 7 trial, the difference being 1.2 months for the
 8 taxane-anthracycline group.

9 So I think that, as treating clinicians, we
 10 have to ask ourselves, what are we doing in terms
 11 of helping patients? Simply delaying a change in a
 12 CT scan by a month or two, I think we would all
 13 agree is not a major finding unless it is
 14 accompanied by other improvements in terms of how
 15 the patient is doing or increased survival.

16 So it's hard for me to look at these
 17 confirmatory trials and to view them as being
 18 clinically relevant or clinically important; and,
 19 hence, it's difficult to look at these as
 20 confirming what was considered to be, as I think
 21 Dr. O'Shaughnessy or Dr. Horning may have said, was
 22 the most remarkable delta progression-free survival

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1 in up-front metastatic breast cancer that had ever
 2 been seen, that had come out of the E2100 trial.

3 DR. MIDTHUN: Other comments? Dr. Logan?
 4 DR. LOGAN: Well, certainly, there's a
 5 number of ways of measuring clinical benefit. I
 6 just want to address each of those in turn. First
 7 of all, survival is the clearest determination of
 8 clinical benefit, and this has been skirted around
 9 the issue by the company in a number of ways.

10 Right now, given the totality of the data,
 11 there is no evidence that Avastin extends the lives
 12 of women with metastatic breast cancer. We have
 13 data from 2400 patients, over four randomized
 14 trials to support this.

15 Although the company has pointed out, on a
 16 number of occasions, that each individual trial is
 17 not powered to detect an overall survival
 18 difference, the combined data certainly is powered
 19 to detect a meaningful difference in overall
 20 survival, but no difference has been detected.

21 The accelerated approval was based on
 22 progression-free survival as a measure of clinical

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1 benefit. Drug approvals based on progression-free
 2 survival as a primary endpoint take us down a
 3 slippery slope, as we've seen in this meeting, for
 4 a number of reasons. It's difficult to pinpoint a
 5 precise magnitude of benefit in progression-free
 6 survival which outweighs the toxicities of the
 7 drug. And we've certainly seen differing opinions
 8 on what kind of magnitude of benefit is
 9 appropriate. Furthermore, issues in study design
 10 and conduct, such as unblinded trials, missing
 11 scans, so forth, can make it difficult to obtain an
 12 accurate estimate of the magnitude of the treatment
 13 benefit.

14 Although, certainly a number of sensitivity
 15 analyses have been conducted by both the sponsor
 16 and the FDA to examine the reliability of the
 17 magnitude of the treatment effect on progression-
 18 free survival, the variability in estimates from a
 19 single trial, which was conducted, the E2100 trial,
 20 as well as these design issues, generate some
 21 uncertainty in the magnitude of the effect on
 22 progression-free survival.

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1 could have been worded is do these two trials
 2 invalidate the results of the first study?
 3 I think the answer to that primarily gets
 4 down to the hypothesis presented as to whether this
 5 was a combination-specific effect. That is, that
 6 it was an effect that was seen with paclitaxel;
 7 it's not going to occur with other drugs.
 8 Clearly, it's difficult to make that
 9 decision with the amount of data presented here.
 10 And I think that question relates potentially more
 11 to the last question we're going to address than
 12 maybe it does to this one, as to whether we
 13 continue to believe the results of the first study,
 14 and therefore think that, at least in one setting,
 15 there's potentially some benefit, or do we take the
 16 data as a whole here and say that, since we
 17 couldn't confirm that in the additional studies,
 18 then there must have been something wrong with the
 19 first one.

20 Now I understand that from a regulatory
 21 perspective we like to have two positive studies.
 22 I think the issue's going to be which of these we

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1 Now, we've seen three subsequent trials that
 2 have all failed to confirm the magnitude of benefit
 3 with differences in median progression-free
 4 survival, between 1 to 3 months, compared to the
 5 original 5.5 months. So we certainly need to
 6 consider that this is a substantial reduction in
 7 the clinical benefit compared to what was
 8 originally seen in the E2100 trial.

9 As I mentioned, it is difficult to pinpoint
 10 a precise magnitude of benefit which outweighs the
 11 toxicities of the drug. I think it's important to
 12 keep in mind that direct and thorough measurement
 13 of patient-reported outcomes and quality of life
 14 can help elucidate that potential tradeoff between
 15 prolonged progression-free survival and increased
 16 toxicity. But this is not done to a satisfactory
 17 degree in the trials that have been conducted so
 18 far. So there is no evidence of a potential
 19 quality of life benefit.

20 DR. MIDTHUN: Dr. Balis?
 21 DR. BALIS: I think that this question could
 22 have been worded in two ways. The other way it

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1 believe more so than whether we verified or not it
 2 was positive.

3 The other part of this, I think, and one of
 4 the difficulties in answering the question about
 5 what was significant, in terms of a magnitude, the
 6 difficulty there is because that is such a
 7 subjective thing. And I think none of us sit in
 8 the position to be able to say what is significant
 9 in terms of additional life that's provided to
 10 somebody that has this disease. And I think that
 11 makes it very difficult to draw a line as to where
 12 you decide it's not worth it or it is worth it.

13 DR. MIDTHUN: Thank you.
 14 Dr. Freedman?
 15 DR. FREEDMAN: Now, I think a lot of this
 16 revolves around what efficacy means, and what does
 17 it mean to the physicians, and what does it mean to
 18 the patients. It cannot be an abstract or
 19 statistical concept by itself. The statistics
 20 certainly help to support or refute. But in this
 21 case, we've got a number of trials which were put
 22 forward, which were put forward in order to verify

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1 and also describe the amount of benefit that there
 2 was observed in the first trial. And for whatever
 3 reasons, whether there were issues with the first
 4 trial, the way it was designed or not, or whether
 5 it was that the other trials also had some issues
 6 with them, they just didn't meet the standard of
 7 showing an improvement in magnitude that we could
 8 then inform better, patients, so that they could be
 9 better informed in making decisions with their
 10 physicians.

11 There's a lot of stress placed, and quite
 12 rightly so, because there's a mandate that the
 13 label and the information that's attached to the
 14 label should be accurate. It should reflect what
 15 we know and it should also reflect what we don't
 16 know.

17 The issue that's come up here is that now
 18 having done these additional trials, we have some
 19 doubts -- and this is not just within this hole; it
 20 goes outside -- about whether the first trial
 21 accurately represents what's written in the label,
 22 not so much in terms of toxicity, because I think

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1 the toxicity information is quite known.

2 However, it's important to realize that it's
 3 a benefit-risk issue when you look at toxicity. If
 4 the efficacy changes and turns out to be not as
 5 much as was thought of originally, then the risk-
 6 benefit ratio must change. Then there may be less
 7 tolerance for the degree of toxicity or the
 8 severity of the toxicity.

9 This is not something that's easily
 10 measured. It's a judgment decision. When you look
 11 at risk and benefit, these people who look at
 12 things reasonably and look at it from the point of
 13 view of the physician and also from the patient,
 14 how do they understand the results of the
 15 discussion that's going on here?

16 The fact that we're having to discuss it
 17 here -- obviously, it's a controversial issue
 18 across many physicians and also patients, as we've
 19 heard. But, ultimately, the FDA's role is to
 20 protect the public and to make a judgment decision
 21 based on the information that they have, or do not
 22 have, as to what is right.

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1 I think the sponsor's raised -- or Genentech
 2 has raised the issue of vulnerability. And
 3 vulnerability is a factor that affects patients.
 4 And it affects patients most when they don't have
 5 the full information presented in an objective
 6 fashion so that they can make the right decision
 7 for themselves.

8 So when I look at this now, we have to now
 9 include the issues that are raised now by the
 10 Ribbon 1 and the other trial, because you cannot
 11 ignore them. The information from those trials is
 12 not currently represented in any labeled
 13 information, obviously. But it's important, and
 14 it's important to assist the patients and their
 15 physicians in making the decision.

16 So I am concerned that at this moment, the
 17 two trials that have been done have raised more
 18 questions than provided answers or clarity about
 19 the information that we have.

20 DR. MIDTHUN: Dr. Sekeres?

21 DR. SEKERES: Thank you. A lot of time has
 22 been spent about the issue of progression-free

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1 survival and separating magnitude of benefit versus
 2 statistical significance. The subsequent studies
 3 that followed the initial one that led to
 4 accelerated approval didn't show the same magnitude
 5 of progression-free survival.

6 I find it difficult to believe that anybody,
 7 if you just take an honest person view of this,
 8 would think that, well, as long as I have a
 9 significant progression-free survival, that should
 10 be enough to satisfy the FDA and to satisfy ODAC
 11 for full approval. And, obviously, that didn't
 12 happen.

13 So we can debate exactly who said what at
 14 the original ODAC meeting and what was communicated
 15 between the FDA and the company, but an honest
 16 person would take a step back and say, you know,
 17 they're probably looking for about the same
 18 magnitude of progression-free survival.

19 Regarding the issue of hazard ratios and
 20 focusing on hazard ratios to the exclusion of
 21 median progression-free survival, the two are
 22 complementary. I understand hazard ratios from a

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1 statistical perspective, and I understand how
2 progression-free survival can vary slightly,
3 depending on what exactly is happening to the
4 curves and whether they're pinching in at exactly
5 the median or not. It won't vary significantly.
6 But I'd actually like to ask
7 Dr. O'Shaughnessy a question, if that would be
8 okay.
9 No one in this room would doubt that you're
10 a fantastic breast cancer doctor. How would you
11 explain to a patient a hazard ratio of .6 for
12 progression-free survival when you're consenting
13 her for chemotherapy?
14 DR. O'SHAUGHNESSY: The way I understand
15 progression-free survival is I really have grown up
16 always looking at the entire curve. And what that
17 means to me and to my patient is that at any time
18 along that curve, the average reduction in her risk
19 of progressing will be 40 percent, for example.
20 I don't discuss medians with patients. I
21 mean, I really don't. I just say, the data
22 show -- obviously, I'm making a recommendation to

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1 her based on her individual disease, of course, but
2 my opinion is that you've got the kind of disease
3 that would likely benefit. But for every step
4 along that curve, no matter where you end up
5 being -- because I don't know where she's going to
6 end up being -- that she's going to have whatever
7 that relative reduction in risk of progression is.
8 So I'm a total curve person.
9 DR. SEKERES: So I'm trying to think this
10 through practically because I see patients just
11 like you do and have these sort of conversations
12 about the relative benefit of a therapy.
13 So if I were a patient hearing that, and I
14 heard a 40 percent reduction at any point in that
15 curve, I would think, gee, well, that sounds like
16 it's 40 percent less likely that my breast cancer
17 would come back.
18 DR. O'SHAUGHNESSY: No, no. In terms of the
19 likelihood of progression, length of progression-
20 free survival, so keeping the disease under
21 control. It's a disease-control issue. How long
22 will it be before I have to face a bad scan?

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1 DR. SEKERES: So how long would it be? That
2 sounds like a time of progression-free survival,
3 which gets to a median.
4 DR. O'SHAUGHNESSY: No, no; at every point
5 along the curve, though, because we don't know
6 whether she's going to be a median, or a quick
7 progressor, or a late progressor, but the average
8 reduction in her risk of progression is going to be
9 40 percent at any time along that curve.
10 So I don't know where she's going to fall,
11 but it's so meaningful to patients to have a scan
12 that's okay, so she doesn't have to go onto
13 something else. And that's important. And that's
14 something that isn't in our classical clinical
15 benefit list, but that's important.
16 But the main reason I recommend it to a
17 patient is I think that for her particular disease,
18 that that progression-free survival is going to be
19 meaningful to her in the context of her risk for
20 symptoms or other -- and organ failure.
21 DR. SEKERES: Again, I agree with you. I
22 would have explained progression-free survival the

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1 same way. I think my patients, at least in my
2 experience, need something else to hang onto.
3 Hearing they have a 40 percent less chance at each
4 time they get a scan isn't going to satisfy
5 somebody. They're not going to walk away from that
6 interaction thinking, okay, so I have how long
7 before my breast cancer comes back.
8 In terms of meaningful to patients, at face
9 value, that seems like that would be true, yet the
10 quality of life studies that have been conducted
11 adjunct to the therapeutic aspects of the trials
12 haven't validated that at all.
13 So I'm done with my thinking about this.
14 Thank you.
15 DR. MIDTHUN: Ms. Portis?
16 DR. COMPAGNI-PORTIS: I know that this is a
17 very emotional issue, and I concur with what
18 Dr. Balis said, that any amount of time is
19 meaningful for patients. And yet, what we have to
20 do today is respond to the research that's been
21 presented to us.
22 I think, after the E2100 studies were

<p style="text-align: right;">Page 225</p> <p>1 presented, there was reason for many to be hopeful, 2 despite the shortcomings in that research that we 3 discussed at that time. And I think we all wanted 4 Avastin to succeed. And the reality is, these 5 studies that we're talking about here in Question 1 6 did not confirm that. These studies didn't bear 7 out this hope. 8 Certainly, .8 months of progression-free 9 survival doesn't translate into a better quality of 10 life or more overall survival, even if that 11 survival is short, which is meaningful to patients. 12 I think that these studies absolutely didn't bear 13 out that hope. 14 DR. MIDTHUN: Dr. Wilson? 15 DR. WILSON: I wanted to go back to a 16 statement Dr. Balis made, which I thought was an 17 interesting one. And that is, do these studies not 18 support, invalidate the results of E2100 or simply 19 not support it? 20 I think that's a real key issue here because 21 it really gets at the fundamental basis of how the 22 accelerated approval system works.</p>	<p style="text-align: right;">Page 227</p> <p>1 apple, and I don't think that's in the patient's 2 best interest. 3 DR. MIDTHUN: Are there any other points for 4 discussion before we move on to vote? 5 [No response.] 6 DR. MIDTHUN: If not, then I will ask you to 7 vote. Again, a yes vote means that you find that 8 the AVADO and Ribbon 1 trials failed to verify the 9 clinical benefit of Avastin for the breast cancer 10 indication at issue in this hearing. CDER asks for 11 a yes vote. Genentech asks for a no vote, and I'll 12 ask you to vote simultaneously. Thank you. 13 [Votes taken.] 14 DR. MIDTHUN: Now, I'll ask each of you to 15 state your name and explain how you voted and why 16 you voted that way. 17 Dr. Wilson, would you like to start? 18 DR. WILSON: Yes. My name is Wyndham 19 Wilson. I voted yes because there were two 20 agreed-to or there were two confirmatory trials 21 that were mandated ongoing, whatever the regulatory 22 language is, to confirm the preliminary results</p>
<p style="text-align: right;">Page 226</p> <p>1 Accelerated approval, as you all know, is a 2 mechanism to bring drugs forward that look to have 3 reasonable likelihood of helping, but for whom we 4 don't have adequate medical or statistical 5 certainty of clinical benefit. And the only way 6 that we're going to be able to do that in a 7 reasonable fashion is to be mindful of the studies 8 that follow. And if those studies confirm, then 9 the drug becomes full approved. If those studies 10 do not confirm, then statistically we have multiple 11 studies. The original one, which was only 12 conditional, has not been shown to be confirmed, 13 and, hence, I don't believe it's a matter of 14 proving or disproving the original study. It is 15 simply, as has been said here multiple times, the 16 totality of the data. 17 If, in fact, we always start to second-guess 18 without compelling reasons the follow-on studies 19 and say, well, maybe the original one was right and 20 the following ones are wrong, we basically may as 21 well give up the accelerated approval, because as 22 was said, we're going to get multiple bites at the</p>	<p style="text-align: right;">Page 228</p> <p>1 from the E2100. 2 I believe, based on the results of those 3 trials, in the absence of a survival benefit or 4 improvement of quality of life, that delaying 5 progression on a CT scan, absent anything else that 6 we can point to, for just a month or two, given the 7 toxicity of this agent, not to mention the fact 8 that quality of life does involve the number of 9 times you come into the hospital, et cetera, which 10 is going to be much greater in the patients who get 11 proteinuria, hypertension, et cetera, I did not 12 feel that these two studies confirmed clinical 13 benefit. 14 DR. MIDTHUN: Dr. Freedman? 15 DR. FREEDMAN: I basically have the same 16 reasons. I felt that they did not verify the 17 magnitude and did not describe any better the 18 clinical benefits that are expected of this Avastin 19 with paclitaxel. 20 DR. MIDTHUN: Ms. Portis? 21 DR. COMPAGNI-PORTIS: Yes. I'm Natalie 22 Compagni-Portis, and I voted yes. I feel that</p>

<p style="text-align: right;">Page 229</p> <p>1 these studies did not confirm E2100 and did not 2 show significant clinical benefit. And they failed 3 to show an increase in overall survival or an 4 increase of quality of life, and that the risk of 5 serious adverse events and risks of deaths were 6 significant.</p> <p>7 DR. LOGAN: Brent Logan. I voted yes. The 8 subsequent studies failed to confirm the magnitude 9 of benefit that was seen in the original study, and 10 there was no additional information of a benefit in 11 overall survival or quality of life.</p> <p>12 DR. MIDTHUN: For the record, that was 13 Dr. Logan speaking.</p> <p>14 Dr. Sekeres?</p> <p>15 DR. SEKERES: This is Mikkael Sekeres. I 16 also voted yes. Unfortunately, the follow-up 17 trials, which were supposed to have been 18 confirmatory, did not confirm the magnitude of 19 progression-free survival, and in my mind, didn't 20 validate that as a clinical endpoint by 21 demonstrating any improvement in overall survival 22 or quality of life.</p>	<p style="text-align: right;">Page 231</p> <p>1 quality of life, since I think we're going to have 2 difficulty with overall survival as a potential 3 endpoint. One of the points that was made as a 4 secondary endpoint was that the drug produced more 5 objective responses than the chemotherapy alone.</p> <p>6 From Dr. O'Shaughnessy's talk, I gather that 7 most of these patients who are treated with the 8 drug are symptomatic at the time they get it. And 9 the question I have for her is, is response a 10 surrogate for relief of symptoms in these patients?</p> <p>11 DR. O'SHAUGHNESSY: Yes. Response rate can 12 be helpful for two groups of patients, one, those 13 who are already symptomatic; there's no question. 14 The higher the response rate, the higher the 15 percentage of patients who will get clinical 16 benefit, relief of symptoms.</p> <p>17 The other group are people who if they do 18 not get a response, that within a relatively short 19 period of time, they will have significant 20 symptoms, or threatening end organ functions. A 21 response for those patients as well, I believe, 22 translates into clinical benefit.</p>
<p style="text-align: right;">Page 230</p> <p>1 DR. MIDTHUN: Dr. Balis?</p> <p>2 DR. BALIS: Frank Balis. I agree with the 3 people here in the panel that the clinical 4 significance of the statistical -- the valid change 5 wasn't enough to validate or verify the outcome of 6 the first study.</p> <p>7 DR. MIDTHUN: Dr. Curt, I know that you were 8 not able to vote, but would you like to express an 9 opinion?</p> <p>10 DR. CURT: No. I don't think that would be 11 appropriate.</p> <p>12 DR. MIDTHUN: Thank you.</p> <p>13 For the record, the voting for Issue 1 was 14 six yes votes, zero no votes, zero abstentions.</p> <p>15 We'll now move onto Issue 2.</p> <p>16 Question 2(a). Does the available evidence 17 on Avastin demonstrate that the drug has not been 18 shown to be effective for the breast cancer 19 indication for which it was approved? This is now 20 open to discussion.</p> <p>21 Dr. Balis?</p> <p>22 DR. BALIS: We talked a little bit about</p>	<p style="text-align: right;">Page 232</p> <p>1 So I think those are the two places, so that 2 doesn't mean everybody, but it means those 3 particular patients with usually symptomatic, more 4 rapidly advancing disease.</p> <p>5 DR. MIDTHUN: Dr. Sekeres?</p> <p>6 DR. SEKERES: Can I ask a follow-up 7 question, Dr. O'Shaughnessy? So did response 8 correlate with an improvement in the FACT-B scores 9 in those patients?</p> <p>10 DR. O'SHAUGHNESSY: I'm going to have to 11 turn to Genentech here to ask them about that.</p> <p>12 DR. REIMANN: As you know, response can 13 happen at different time points on the study, and 14 the FACT-B instrument was collected also at 15 different time points of the study. So we don't 16 have a correlation between changes in FACT-B score. 17 We did look, but we didn't see a correlation, but 18 it is a bit challenging, based on the timing of the 19 FACT-B and the timing of the tumor assessments.</p> <p>20 DR. SEKERES: Though, presumably, people who 21 were responding at one time point would be 22 responding to when the next FACT-B would be</p>

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1 administered to those patients?
 2 DR. REIMANN: We don't have a correlation of
 3 FACT-B changes and objective response rate in
 4 AVADO.
 5 DR. SEKERES: So there is no correlation
 6 between a validated instrument measuring quality of
 7 life and response to Avastin?
 8 DR. REIMANN: It is a valid instrument in
 9 assessing quality of life. I think the question
 10 is, is it sensitive in this patient population? In
 11 a front-line setting, in a typical front-line
 12 population, probably fewer than 20 percent of
 13 patients are symptomatic. And that's the studies
 14 that are done by any sponsors. They have a mixture
 15 of ECOG zero and 1 patients. So I think you'd
 16 really want to focus on symptomatic patients, and
 17 that's a smaller group.
 18 DR. SEKERES: So I think probably, the best
 19 instrument out there for measuring quality of life,
 20 in the U.S. at least, is the FACT for a number of
 21 different cancers, including breast cancer. And we
 22 don't have a clear correlation between improvement

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1 in a woman's well-being, how she reports it herself
 2 and response to a drug.
 3 I was once taught that the plural of
 4 anecdote is not data. So we each have one story of
 5 somebody who felt better while responding, but if
 6 the facts don't support that, then that's not
 7 something that we can rely on.
 8 DR. MIDTHUN: Other comments? Dr. Wilson?
 9 DR. WILSON: I think this is a very slippery
 10 slope. Response is an arbitrary number determined
 11 by the RECIST, and it's got a threshold. We all
 12 oncologically know well that patients can have
 13 significant improvement in symptoms without hitting
 14 a response endpoint. And so I just want to echo
 15 what Dr. Sekeres said, and that is that, yes, if
 16 you have a PR or more and you're symptomatic, then
 17 the chances are you will have amelioration of your
 18 symptoms. However, you can have amelioration of
 19 bone pain, et cetera, without a bona fide PR. And
 20 so I think that you can't use the response numbers
 21 as a surrogate for that.
 22 Then, of course, that's confounded by the

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1 fact that only a minority number of folks, I
 2 understand, even had a truly symptomatic disease.
 3 So I think we're back to ground zero in terms of,
 4 we have no evidence that the treatment arm improved
 5 quality of life.
 6 DR. MIDTHUN: Any other comments,
 7 discussion? If not, then I think we're ready to
 8 vote on Question 2(a), does the available evidence
 9 on Avastin demonstrate that the drug has not been
 10 shown to be effective for the breast cancer
 11 indication for which it was approved? CDER asks
 12 for a yes vote. Genentech asks for a no vote.
 13 We'll now vote simultaneously.
 14 [Votes taken.]
 15 DR. MIDTHUN: For the record, the results of
 16 voting to Issue 2(a) are six yes votes, zero no
 17 votes, zero abstentions. I'll ask each of you to
 18 state your name, your vote, and why you voted that
 19 way.
 20 Dr. Wilson, would you like to start?
 21 DR. WILSON: Wyndham Wilson, this really is
 22 a variation on the first question. I suppose one

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1 could have looked at it as somewhat different. But
 2 this really gets out what Dr. Balis said, which is
 3 did the subsequent studies invalidate the original
 4 study.
 5 I think that's obviously at the heart of
 6 what we are discussing here. However, the way the
 7 accelerated approval system is set up -- and I
 8 think it's a very good one -- is that the
 9 subsequent studies need to validate the original
 10 study, and in my view, the subsequent studies did
 11 not. And, hence, the original accelerated
 12 approval, in my view, was not confirmed, and,
 13 hence, I voted yes.
 14 DR. MIDTHUN: Dr. Freedman?
 15 DR. FREEDMAN: Ralph Freedman, I voted yes
 16 on a similar basis, that the totality of the data
 17 do not show a clinical benefit in the absence of
 18 anything else that we can get our hands around.
 19 I think the issue, again, is to look at the
 20 changing risk-benefit ratio, which changes as a
 21 result of doubts that are now raised. And they
 22 alter the threshold for acceptance of toxicity in

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1 relation to benefit, at this point.
2 DR. MIDTHUN: Ms. Portis?
3 DR. COMPAGNI-PORTIS: Yes. This is Natalie
4 Compagni-Portis. I voted yes for the same reasons.
5 The research evidence does not demonstrate a
6 clinical benefit. And even though we have
7 anecdotal information, we don't show any
8 improvement in quality of life or in overall
9 survival.
10 DR. MIDTHUN: Dr. Logan?
11 DR. LOGAN: Brent Logan, I voted yes for
12 many of the same reasons as in the prior question.
13 The totality of the data suggests no survival
14 benefit, a very modest improvement in progression-
15 free survival, which has questionable clinical
16 relevance, and no evidence of a benefit in quality
17 of life.
18 DR. MIDTHUN: Dr. Sekeres?
19 DR. SEKERES: I'm Mikkael Sekeres. I voted
20 yes as well. And I define efficacy in this setting
21 as progression-free survival of significant
22 magnitude coupled with a quality of life advantage

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1 or an overall survival advantage, and Avastin
2 didn't achieve either of those definitions for
3 efficacy.
4 DR. MIDTHUN: Dr. Balis?
5 DR. BALIS: Frank Balis, I think, in looking
6 at this question, it obviously is asking you about,
7 again, the totality, what the outcome was, not just
8 in one study, but in all of the studies. And
9 effectiveness, I agree, it needs to be something
10 more than a fairly short increase in progression-
11 free survival. So for that reason, I voted yes
12 also.
13 DR. MIDTHUN: We will go on now to
14 Question 2(b).
15 Question 2(b). Does the available evidence
16 on Avastin demonstrate that the drug has not been
17 shown to be safe for the breast cancer indication
18 for which it was approved and that Avastin has not
19 been shown to present a clinical benefit that
20 justifies the risk associated with use of the
21 product for this indication?
22 CDER asks for a yes vote. Genentech asks

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1 for a no vote. So we'll now open this up to
2 discussion.
3 Dr. Freedman?
4 DR. FREEDMAN: I had a question that I
5 wanted to ask Genentech, if I may, and that relates
6 to the burden for these patients. It's something
7 that's very hard to measure. And I'm clearly not
8 talking about financial. What I'm talking about is
9 the physical burden to subjects.
10 I wanted to know whether Genentech collected
11 any information in E2100, or any of the others for
12 that matter, about the frequency of
13 hospitalizations that these patients had to undergo
14 in the different arms of the studies, and if
15 they've got information on the median duration of
16 hospitalizations. I'm specifically referring to
17 hospitalizations relating to SAEs.
18 DR. HORNING: The data were collected in the
19 AVADO study, and there was no difference in
20 hospitalizations.
21 DR. FREEDMAN: Do you have the information
22 on the median duration of hospitalizations?

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1 DR. HORNING: I don't have the information
2 on the median duration of hospitalization at this
3 time.
4 DR. MIDTHUN: Can I ask just a follow-up
5 clarification? So were those data collected only
6 in the AVADO study, the hospitalization data?
7 DR. HORNING: Yes.
8 DR. MIDTHUN: Thank you.
9 Dr. Wilson?
10 DR. WILSON: You may not have this, but with
11 the increased incidence of hypertension,
12 proteinuria, these would require more doctor visits
13 to control blood pressure, to monitor, et cetera.
14 Was data collected on the two arms with
15 regard to visits related to these various side
16 effects?
17 DR. REIMANN: I don't believe we collected
18 specific information on doctor visits, but of
19 course, on clinical trials, patients are being seen
20 quite regularly.
21 DR. WILSON: I'm sorry. Could you say that
22 again? I didn't understand it.

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1 DR. REIMANN: We didn't collect that
2 specific information, but, of course, based on the
3 frequency of chemotherapy, patients are coming in
4 typically every two or three weeks.
5 DR. WILSON: Well, that might not explain
6 regulation of high blood pressure, et cetera.
7 DR. HORNING: The answer is that we do not
8 have specific data with regard to that, but
9 perhaps, because we have a very experienced
10 clinician, she could comment.
11 DR. O'SHAUGHNESSY: The patients don't have
12 to make any extra trips to the office for
13 hypertension or proteinuria monitoring. When you
14 first pick up the blood pressure, you actually ask
15 them to verify it. You ask them to get the home
16 blood pressure monitor. You ask them to write it
17 down, take it at different times of the day, bring
18 it to you, which they do at their next visit.
19 Then it's pretty routine to get a urinalysis
20 pretty much at the beginning of every cycle, so
21 they're not coming in extra for that. So the blood
22 pressure monitoring is done probably fairly

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1 frequently because they're coming in to see the doc
2 every -- once a month on this particular regimen,
3 but no extra trips.
4 DR. MIDTHUN: Ms. Portis?
5 DR. COMPAGNI-PORTIS: We have heard
6 repeatedly that the risks involved are usual, and
7 that they're manageable, and even that they're
8 similar to other drugs that are given for
9 metastatic breast cancer, but it seems to me that
10 the adverse effects of Avastin are significant, and
11 the studies do show this; that the risks even
12 include death without any demonstrated benefit.
13 Again, I know we've heard from those who say
14 that the symptoms are tolerable, but as Dr. Sekeres
15 pointed out, those anecdotes are not evidence. And
16 so I think that the risks are considerable, and
17 that we shouldn't minimize those risks; that they
18 are very important and that we're not hearing from
19 patients who have really suffered because of the
20 drug.
21 DR. MIDTHUN: Any other? Dr. Wilson?
22 DR. WILSON: I guess from a philosophical

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1 perspective, when I went through medical school, it
2 was always do no harm. If a drug had no side
3 effects but I could not determine any real
4 meaningful clinical benefit, in my view, that drug
5 should not be given to somebody.
6 This is not the case here. In this case, we
7 have a totality of data to confirmatory trials,
8 that while different people may look at them
9 differently, I think reasonable people would agree
10 that a month or so prolongation in progression free
11 is not really a meaningfully beneficial endpoint.
12 It's not really beneficial. And, yet, we all have
13 heard that the side effects of the Avastin in these
14 trials are similar to those that have been
15 described in the package insert and in the black
16 box warning, which while different from
17 chemotherapy can be very, very serious and lead to
18 acute death. So that's the way I look at this.
19 DR. MIDTHUN: If there is no more
20 discussion, I think we're ready to vote. We'll
21 vote simultaneously.
22 [Votes taken.]

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1 DR. MIDTHUN: For the record, the voting
2 results on issue 2(b) are six yes votes, zero no
3 votes, zero abstentions. And I'll ask each
4 panelist to indicate how they voted and why they
5 voted that way, and this time, I'll start with
6 Dr. Balis.
7 DR. BALIS: This is Frank Balis, and I voted
8 yes. And I think it was quite striking, the
9 disparity of the way these data were interpreted,
10 the toxicity data. I think, in large part,
11 obviously, it depends on the perspective that one
12 has, but it's reflected I think in the way that the
13 data, which should be relatively factual, was
14 interpreted by the two sides that they presented
15 here, as to whether this was tolerable or a scourge
16 to humanity, in terms of the degree of toxicity
17 that it had. And I'm sure it probably falls
18 somewhere in between.
19 But I think what it gets down to here is
20 that if we don't think it's effective, then we
21 can't tolerate any toxicity from it. And there
22 clearly is at least some, even from the best

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1 perspective in terms of how it's presented. So for
 2 that reason, I voted yes.
 3 DR. MIDTHUN: Dr. Sekeres?
 4 DR. SEKERES: I am Mikkael Sekeres, and I
 5 also voted yes. For therapies for cancer, we are
 6 willing to accept a high rate of toxicity because
 7 the diseases we are treating are so awful. But
 8 that is predicated on therapy being effective.
 9 We voted in the previous question on whether
 10 or not this therapy was effective for metastatic
 11 breast cancer, and we all agreed it was not
 12 effective. Given that, we cannot tolerate a
 13 13 percent higher rate of serious toxicities.
 14 DR. MIDTHUN: Dr. Logan?
 15 DR. LOGAN: Brent Logan, I voted yes.
 16 Avastin resulted in a significant increase in
 17 grade 3 to 5 toxicities. These toxicities
 18 certainly have an adverse impact on patient quality
 19 of life. And the modest magnitude of benefit in
 20 progression-free survival that we have seen in the
 21 combined data is not substantial enough to justify
 22 this additional toxicity.

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1 DR. MIDTHUN: Ms. Portis?
 2 DR. COMPAGNI-PORTIS: Natalie Compagni-
 3 Portis, and I voted yes. The evidence that was
 4 presented to us demonstrates that there is a high
 5 risk to patients with little or no demonstrated
 6 clinical benefit. And I think we can only ask
 7 patients to take on this risk when there is
 8 significant benefit to them.
 9 DR. MIDTHUN: Dr. Freedman?
 10 DR. FREEDMAN: Ralph Freedman, I voted yes.
 11 I think we accept the fact that the toxicity
 12 information attached to the label indications has
 13 little change between the studies. However, what
 14 has now changed is the risk-benefit evaluation.
 15 And this is based on the fact that you have at
 16 least additive toxicities now that are being
 17 considered in relation to a clinical benefit, in
 18 quotes, "that is less well defined and less clear."
 19 And it's certainly not better described by the
 20 postmarketing studies that are being submitted.
 21 As I've said, these uncertainties about the
 22 effectiveness alters now the risk-benefit ratio to

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1 a point at which one can less tolerate the effects
 2 that have been described, the toxicity effects.
 3 DR. MIDTHUN: Dr. Wilson?
 4 DR. WILSON: Wyndham Wilson, in the absence
 5 of clinical benefit, I do not believe any toxicity
 6 is acceptable, and I voted yes.
 7 DR. MIDTHUN: We'll now go onto the last
 8 issue. Question 3. If the Commissioner agrees
 9 with the grounds for withdrawal set out in Issue 1,
 10 Issue 2(a), or Issue 2(b), should FDA nevertheless
 11 continue the approval of the breast cancer
 12 indication while the sponsor designs and conducts
 13 additional studies intended to verify the drug's
 14 clinical benefit?
 15 Genentech asks for a yes vote. CDER asks
 16 for a no vote. This is now open for discussion.
 17 Dr. Wilson?
 18 DR. WILSON: May I ask Genentech, as well
 19 as --
 20 DR. MIDTHUN: Yes.
 21 DR. WILSON: -- perhaps CDER, a question?
 22 One of the reasons in the postmarketing

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1 trials that are done following accelerated
 2 approval, that the clinical trials are not done in
 3 the exact same setting, is because it is very
 4 difficult to get patients to agree to be randomized
 5 to a therapy that has had at least accelerated
 6 approval, making the conduct of those trials very,
 7 very difficult.
 8 I guess I have heard from Genentech the
 9 length of time that they think that they could do a
 10 randomized study with biomarkers, with paclitaxel.
 11 However, I really haven't heard a really good
 12 assessment of how this is going to be impacted by
 13 the indication still being approved. It seems to
 14 me that it will be extremely difficult to accrue to
 15 such a trial in the United States and Europe. And,
 16 hence, will this not be required to be done outside
 17 of the West; and, number two, will it not make it
 18 significantly longer before we have any answers,
 19 and therefore expose patients to even longer
 20 periods of risk if, in fact, the confirmatory trial
 21 turns out to be negative?
 22 If CDER and Genentech could just give us

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1 some sense of this because I don't think the
2 timeline they presented -- I think the timeline
3 they presented was more in line with what you would
4 have expected for the original study.
5 DR. MIDTHUN: Does Genentech want to go
6 first?
7 DR. HORNING: The timeline that was
8 presented is based upon our preliminary
9 feasibility. It is not based upon the accrual to
10 the original E2100 study. As you heard earlier
11 today, the feasibility at this point is
12 preliminary, and we anticipate that we'll have
13 final feasibility in July.
14 With regard to accrual, we also stated
15 earlier today that we anticipate that the majority
16 of patients will be accrued outside the United
17 States. For those within the United States, we
18 have discussed, among ourselves and advisors, about
19 the feasibility of accrual if the indication is
20 withdrawn or the indication is left such that a
21 confirmatory trial is ongoing. And we heard from
22 breast cancer experts that there are pros and cons

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1 to each of those as it relates to feasibility.
2 We do feel that there are individuals in the
3 United States, physicians and patients, who are at
4 relative equipoise on this question and would be
5 willing to participate in a trial, and be, perhaps,
6 more interested in their participation because a
7 biomarker hypothesis is included.
8 With regard to outside the United States,
9 and specifically in Europe, there are places where
10 Avastin is approved, but it's not necessarily
11 accessible. The United Kingdom would be an example
12 of that. There are other places in Western Europe
13 as well.
14 So, overall, the plan is to finalize our
15 feasibility. The feasibility that you heard about
16 earlier today, with the timelines, is based upon a
17 preliminary feasibility, based upon estimates from
18 a CRO that we have worked with extensively. We'll
19 complete the feasibility in July, and the
20 anticipation is that this will be a global trial
21 with participation from the United States, from
22 Western Europe, and elsewhere.

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1 DR. WILSON: May I ask CDER to comment on
2 this? Because, again, the stance with the
3 accelerated approval has not been to do this,
4 because it is not considered to be feasible, so are
5 we being realistic here?
6 DR. JENKINS: I can comment, and then if
7 Dr. Pazdur wants to add. The general practice in
8 oncology has been to look to confirm clinical
9 benefit in either a different disease setting or in
10 a different phase of the disease. I think that
11 goes to the point of why CDER considered AVADO and
12 Ribbon 1 as potential confirmatory trials, because
13 the general pattern is not to repeat the
14 accelerated approval study as the confirmatory
15 study because of concerns about how will patients
16 enroll in a study where they are being asked to
17 forego an FDA-approved treatment option. I brought
18 that up earlier. Dr. Pazdur mentioned to me that,
19 in some cases, trials had already been enrolled at
20 the time of the accelerated approval.
21 In the HIV setting, the pattern that's
22 developed over time is that, basically, the same

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1 trial that serves as the accelerated approval trial
2 is the one that confirms benefit, because we look
3 at an interim analysis at 24 weeks. The trial is
4 ongoing while FDA is reviewing the data and the
5 final decision is made on the 48-week data from
6 that trial.
7 I'll ask Dr. Pazdur if he wants to add
8 anything about any history of other approaches.
9 DR. PAZDUR: My only comment is I feel this
10 is somewhat of a paradoxical situation. On one
11 hand, we're saying, the FDA is saying, this drug is
12 safe and effective in the proposed indication; and
13 then on the other hand, we're saying, let's test
14 that same indication to see if it's safe and
15 effective. It's a paradox.
16 DR. WILSON: So, in FDA's experience of
17 having follow-on studies, have you ever had a
18 situation where you went back and said, well, the
19 new ones weren't working because you did it in a
20 different setting? I mean, this is a very unique
21 circumstance.
22 DR. PAZDUR: I can't think of one off the

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1 top of my head.
 2 DR. MIDTHUN: Yes, Ms. Portis?
 3 DR. COMPAGNI-PORTIS: Just so I understand.
 4 So what safeguards -- if this were to happen, what
 5 safeguards would be put in place to protect
 6 patients in the interim so there could be a period
 7 of time during which patients are continuing to use
 8 this drug? And how would we protect those
 9 patients? How would we collect data about the
 10 impact on these patients?
 11 It just seems that we could have many years
 12 of women using this drug without proof of
 13 effectiveness or without monitoring the dangers. I
 14 don't know. I guess that question is for both the
 15 sponsor and for FDA.
 16 DR. MIDTHUN: Genentech, would you like to
 17 respond first?
 18 DR. HORNING: As we have said earlier, we're
 19 open to working with CDER regarding a potential
 20 path forward to keep this option open for patients.
 21 DR. JENKINS: If I understand your question,
 22 you're asking if it stays as an approved indication

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1 while the confirmatory trial is going on, how will
 2 we monitor what's happening to patients who may
 3 continue to use it under the approved indication?
 4 I think that would have to continue under
 5 the same mechanisms we use now, as far as any
 6 reports that come in for spontaneous adverse
 7 events. I'm not aware of any systematic way of
 8 collecting data from that practice of medicine, use
 9 of the drug.
 10 DR. MIDTHUN: Yes, Dr. Curt?
 11 DR. CURT: I think this is the most
 12 important of the three questions which the
 13 committee has to consider. If the indication is
 14 withdrawn, and the sponsor indeed is able to
 15 confirm the results of E2100 with a preferred
 16 chemotherapy partner that can maintain dose
 17 intensity, then for that interim, patients will not
 18 be able to access, at least in the U.S., a
 19 treatment which prolongs PFS significantly. If, on
 20 the other hand, the indication is maintained and
 21 the sponsor is unable to confirm E2100, then
 22 patients will be exposed to a treatment which has

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1 an overall poor risk-benefit profile.
 2 So in some ways, the sponsor's middle ground
 3 makes some sense, which is to maintain the drug for
 4 use in specific subsets of patients who are likely
 5 to gain the most benefit and have the least harm.
 6 The one thing that I haven't heard in this
 7 meeting was who those patients are, although I did
 8 hear from Dr. O'Shaughnessy that patients with
 9 symptomatic or a more aggressive disease might be
 10 appropriate candidates for open-label treatment.
 11 Does the sponsor have any data to indicate
 12 that patients -- such as the ones that
 13 Dr. O'Shaughnessy describes, more aggressive, more
 14 symptomatic disease -- do better on the combination
 15 than they do on monotherapy with the drug alone?
 16 Are there any patients subsets where you can
 17 answer that question of who's most likely to
 18 benefit, or, just as important, who's least likely
 19 to have toxicity?
 20 DR. HORNING: Well, let me try to rephrase
 21 the question in a different way and see if this
 22 resonates. I think the issues that you heard from

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1 Dr. O'Shaughnessy relate to the heterogeneity of
 2 metastatic breast cancer, and that there are some
 3 patients who are more symptomatic than others,
 4 there are some patients who have higher tumor
 5 burdens, and there are some patients who have fewer
 6 options, simply by virtue of the fact that they
 7 have triple negative disease and they have no
 8 hormonal agent options throughout the course of
 9 their disease.
 10 So if we look at it that way, the patients
 11 that have shorter disease-free intervals, visceral
 12 sites of disease, three or more metastatic sites,
 13 or triple negative, what we see is that in E2100,
 14 that the hazard ratio continues as it is in the
 15 overall study. It's actually slightly lower in the
 16 triple negative patients.
 17 But if you look, overall, at the effect of
 18 Avastin plus chemotherapy, we see an effect in
 19 essentially all subsets, but that includes those
 20 subsets like triple negative patients. And the
 21 patients that are not necessarily called out in our
 22 studies but would fit into the more heavily tumor-

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1 burdened patients, as not necessarily having more
2 response, but they have a response that is similar,
3 they simply have more at stake, if you will, with
4 regard to the status of their disease.
5 DR. CURT: I suppose the issue with that,
6 with regard to the agency, is that this is post hoc
7 unplanned subset analysis, and I wonder how CDER
8 would respond to that sort of middle-ground
9 approach.
10 DR. JENKINS: Thank you. Let me just point
11 out that, generally, when we are talking about the
12 type of labeling that you describe, we like to base
13 it on data suggesting that data from the clinical
14 trials demonstrate that a subgroup has a favorable
15 benefit-risk profile. Dr. Keegan will review some
16 analyses that we have in a back-up slide.
17 DR. KEEGAN: If you could put up back-up
18 slide 59.
19 To start with, there were, as was mentioned,
20 no data collected on symptoms, patient symptoms, at
21 baseline. And the majority of the patients had an
22 ECOG performance status of zero or 1, but we don't

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1 know which of any of those symptoms might have been
2 related to their cancer. So we have no data on
3 whether or not symptomatic patients would benefit
4 or to what degree they would benefit because they
5 simply were not studied.
6 We did do exploratory analyses, looking
7 within each trial and within each independently
8 powered cohort, segregating the triple negative
9 patients from those who were simply HER2-negative,
10 but ER- or PR-positive. And so the triple
11 negatives are designated by the little three dashes
12 at the end of the cohort.
13 As you can see, at least based on survival
14 and the progression-free survival data, subgroup
15 analyses look similar. There are not, for the most
16 part, differences between the treatment effects in
17 patients who are HER2-negative, ER-, PR-positive,
18 and in those who are triple negative. So we don't
19 have any sense that they respond differently than
20 the other.
21 DR. CURT: There is no claim here for
22 overall survival. So the data for PFS looks the

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1 same. Is that right?
2 DR. KEEGAN: Yes. I think that should be
3 one slide before 58. And as I said, I just wanted
4 to mention this for the record, that using the same
5 exploratory subgroup analysis, there doesn't seem
6 to be any difference in terms of treatment effects
7 in the ER-, PR-, HER2-negative subgroup, than for
8 those who are triple negative.
9 DR. MIDTHUN: Dr. Freedman?
10 DR. FREEDMAN: I think Dr. Curt put the
11 dilemma for us very well. It's a question of
12 whether you allow the approval to continue and then
13 potentially do harm to patients versus stopping it.
14 At this point, it's very difficult, in the absence
15 of clear information, that indicates that a subset
16 of patients are benefitting. Even intuitively, one
17 might think, well, because patients have bulky
18 disease and symptoms, they are the ones that are
19 most likely to benefit. Maybe they could do worse,
20 because they would have the disease plus the
21 serious adverse events to deal with, and they would
22 be additive in the case of two drugs.

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1 From my reading of the literature also, it
2 doesn't seem to be that there is clarity amongst
3 oncologists about whether one or two agents are
4 appropriate for this disease.
5 So there's just so many questions here. And
6 I think when you're looking at things in a broad
7 sense and you have to protect, the agency has to
8 look at protecting a larger number of patients,
9 sometimes they have to make a decision that doesn't
10 favor individual patients, but it's on the basis of
11 the whole. And often, you've got to do that when
12 you've got factors that don't help you make the
13 decision clearly.
14 DR. MIDTHUN: Dr. Sekeres?
15 DR. SEKERES: We have tried to slice this
16 pie in a lot of different ways to try to find some
17 kind of benefit for this drug in combination with
18 chemotherapy for a desperate breast cancer
19 population. And no matter which way we look at it,
20 as what were supposed to be confirmatory studies in
21 progression-free survival, looking at toxicity,
22 looking at overall survival, looking for data about

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1 subgroups, all we're left with are crumbs. There's
 2 nothing we can hang our hat on in these studies
 3 that would make me feel comfortable continuing to
 4 expose a lot of patients to risk without a clear
 5 benefit.
 6 DR. MIDTHUN: Dr. Logan?
 7 DR. LOGAN: I think it's important to
 8 remember that the accelerated approval process
 9 should not signal a change in the drug approval
 10 standard. It's just a mechanism to allow faster
 11 access to promising drugs. And part of that is, as
 12 the FDA has argued, they need to be able to
 13 withdraw accelerated approvals.
 14 I think it's important that the label should
 15 reflect a current understanding of the benefit-risk
 16 profile, to provide accurate, up-to-date
 17 information to patients. If the current
 18 understanding of that benefit-risk profile is not
 19 favorable, as we have been discussing here today,
 20 then I think the label should reflect that.
 21 DR. O'SHAUGHNESSY: Dr. Midthun, may I just
 22 respond to the question about the triple negatives?

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1 I would just like to make a comment for the record,
 2 if I might, that the E2100 data showed a point
 3 estimate of .4 on progression-free survival, which
 4 is a 60 percent reduction in the risk of
 5 progression in this very high, unmet medical need
 6 population that has very few other options. Thank
 7 you.
 8 DR. MIDTHUN: Yes, Dr. Balis?
 9 DR. BALIS: Can we ask whether the conduct
 10 of the follow-up study is contingent on the outcome
 11 of this question? Meaning, would it be done no
 12 matter what the answer is?
 13 DR. BARRON: As we stated before, I think we
 14 believe that the data from E2100 was robust and
 15 believe that patients will be best served by
 16 confirming the findings in a subsequent study. And
 17 our current thinking is that we would be, based on
 18 the data we have today, moving forward either way.
 19 DR. MIDTHUN: Dr. Wilson?
 20 DR. WILSON: I think Dr. Logan said it very
 21 well. He said that we have a standard and that we
 22 shouldn't be changing that standard unless we have

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1 a very good reason. I think that -- as I said at
 2 the ODAC when we first looked at this last year, I
 3 said that I felt that Genentech had done an
 4 outstanding job in performing two excellent trials
 5 in a very timely fashion. By virtue of the
 6 accelerated approval process, those two trials do
 7 not confirm the original findings, and, hence, the
 8 withdrawal is indicated.
 9 Having said that, I think to not do that,
 10 you need to have compelling evidence that the
 11 confirmatory trials or the original trial -- there
 12 is something different about them that is above and
 13 beyond anything we've seen before to I think change
 14 the regulatory standard.
 15 We heard from Dr. Pazdur that all other
 16 trials, to his knowledge, that we've
 17 done -- they've done confirmatory trials in other
 18 settings, which is the standard -- that this has
 19 not come up before. So the question is, is there
 20 something compelling about the E2100 trial? And
 21 what has been put forward is a hypothesis that it
 22 is the drug, paclitaxel.

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1 Well, the confirmatory trials used a very
 2 closely related analog, docetaxel. The Ribbon
 3 trial had a taxane arm, which was a combination of
 4 multiple different taxanes, I presume. And so I
 5 think that the confirmatory trials got about as
 6 close to the drug classes that you could possibly
 7 get. And I think it is not a scientifically
 8 rigorous and viable contention that there is just
 9 something magical about paclitaxel that isn't
 10 reflected in these other trials.
 11 So, for me, you need a compelling reason to
 12 deny these other trials and to continue the
 13 indication, and I don't see a scientific one that
 14 is compelling, at least for me.
 15 DR. MIDTHUN: Any other questions?
 16 [No response.]
 17 DR. MIDTHUN: If not, we will move to vote
 18 on Question 3.
 19 [Votes taken.]
 20 DR. MIDTHUN: For the record, there are zero
 21 yes votes, six no votes, and zero abstentions. And
 22 I will now ask each of you to state how you voted,

<p style="text-align: right;">Page 265</p> <p>1 your name, and why you voted the way you did. And 2 I'll start again with Dr. Balis. 3 DR. BALIS: Frank Balis. I voted no on 4 this. I think it's contradictory, as we talked 5 about, to conduct a study to show efficacy at the 6 same time that you leave the drug approved for that 7 indication. Granted, there was a lot of emotional 8 testimony put forward here to keep the drug 9 available. I think the evidence is, at this 10 point -- the burden of evidence, as we talked 11 about -- is there's not enough data to support this 12 continuation of the approval. And, hopefully, the 13 follow-up study will demonstrate to the contrary. 14 DR. SEKERES: I'm Mikkael Sekeres. I also 15 voted no. It gave me pause to continue to make 16 available a drug for an indication when that drug 17 hasn't demonstrated the type of efficacy that women 18 with breast cancer deserve and expose them to 19 serious toxicities. 20 DR. LOGAN: Brent Logan. I voted no. As 21 they indicated earlier, I think the label should 22 reflect the current understanding of the benefit-</p>	<p style="text-align: right;">Page 267</p> <p>1 of clarity on the risk-benefit assessment, the fact 2 that the label indications as exist really no 3 longer adequately represent the current 4 understanding in the light of the subsequent 5 studies, and also the lack of feasibility -- the 6 lack of uncertainty about whether it's feasible to 7 conduct studies, because I feel that probably 8 there's no longer equipoise for this particular 9 issue. And the likelihood that the study will be 10 done and meet its accrual objectives is certainly 11 in doubt. 12 DR. WILSON: Wyndham Wilson. I voted no. I 13 feel the confirmatory trials were extremely well 14 done, used the same class agents, and did not show 15 any reason, any clinically meaningful improvement 16 in progression-free survival or in overall 17 survival. 18 I would encourage the company, if they are 19 in fact convinced that there is a clinical benefit 20 here, to do this follow-up trial as quickly as 21 possible. I would say to, also, patients out there 22 with breast cancer that I think these have been</p>
<p style="text-align: right;">Page 266</p> <p>1 risk profile. And as we've discussed today, our 2 current understanding, given the totality of the 3 data, is that that benefit-risk profile is not 4 favorable right now. s 5 DR. COMPAGNI-PORTIS: Natalie Compagni- 6 Portis. I also voted no. There was some hope that 7 perhaps there was a subset of patients that 8 responded favorably, and it seems that that's not 9 the case. 10 I also was concerned that the likelihood of 11 this study being actually enrolled in a timely way 12 would be compromised, which means that women would 13 continue to be subjected to an unproven treatment 14 with known serious risks, the risk of death, and no 15 guarantee of increased survival or an improved 16 quality of life. 17 DR. MIDTHUN: Dr. Freedman? 18 DR. FREEDMAN: Ralph Freedman. I voted no. 19 I have to say that I struggled with this and 20 struggled with this until just before the meeting. 21 I don't know that people would believe me, but 22 that's true. And, eventually, I felt that the lack</p>	<p style="text-align: right;">Page 268</p> <p>1 extremely important trials, and that I hope that 2 they look at all of the evidence and look to see 3 that, in very large, randomized studies using other 4 very potent taxanes, there was no evidence that 5 this drug was of help to them and not come away 6 feeling as though an important drug that is going 7 to make them feel better or make them live longer 8 is being taken from them. 9 [Audience comments off mic - inaudible.] 10 DR. MIDTHUN: I thank you for your comments. 11 I would now like to -- 12 [Audience comments continued -- inaudible.] 13 Closing Statement by Presiding Officer 14 DR. MIDTHUN: I would now like to move to 15 make closing statements. 16 Thank you for your participation and your 17 attention during this proceeding. This 18 administrative hearing, provided for under our 19 regulations, is a means to prepare a record that 20 will form the basis for the final decision by 21 Commissioner Hamburg. The hearing has also 22 provided an opportunity for the public to observe</p>

1 and participate in the type of difficult decision-
2 making process that the FDA engages in each day as
3 it considers the approval or the withdrawal of
4 approval of drug products.

5 As illustrated by the public presentations
6 at the beginning of the hearing, FDA's focus is
7 always on the effect that our decisions will have
8 on patients who will use those products, including
9 those patients who may be benefited by them and
10 those who may also be harmed by them.

11 In every instance, our decisions are based
12 on the scientific data available to us. The
13 applicants, typically companies that develop the
14 products, are responsible for producing the data
15 upon which decisions are made. They are very
16 knowledgeable about these data and they, thus, play
17 an integral part in informing our decision-making
18 process.

19 Sometimes there are differences of opinion
20 as to what the data mean. When this occurs, we
21 carefully discuss those differences, listen to all
22 points of view, including the view of the

1 recognize the importance of resolving these issues
2 expeditiously.

3 Adjournment

4 DR. MIDTHUN: We very much appreciate the
5 significant efforts that so many people have put
6 into the presentations at this hearing and the high
7 level of discussion that has prevailed. The
8 hearing is now adjourned. Thank you.

9 (Whereupon, at 3:15 p.m., the hearing was
10 adjourned.)

1 applicant, and carefully think through the issues
2 that presented. That was what occurring in a very
3 public way during this proceeding.

4 The record of this hearing will close on
5 July 28th of this year. While we had earlier
6 stated that the docket would close on July 14,
7 Genentech and the Center have jointly requested an
8 opportunity to have until July 28th to submit their
9 final summaries for their respective views on the
10 issues, and I have granted that request.

11 Thus, we will keep the docket open for
12 everyone, including members of the public, to make
13 submissions until July 28th. I will then sit down
14 with Commissioner Hamburg to discuss the record
15 that has been created and the hearing process, and
16 she will make a decision based on all of this
17 information.

18 I will work with Commissioner Hamburg to
19 draft a written document that explains the basis
20 for whatever decision is ultimately reached. I
21 cannot tell you at this point when the decision
22 will be finalized and issued, but we all do

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